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THE PATHOLOGY OF THE PARATHYROID GLAND IN HYPERPARATHYROIDISM *

A STUDY OF 25 CASES

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INTRODUCTION

De Santi [45] was the first to recognize a tumor of parathyroid origin in 1900, twenty years after the discovery of the glands in 1880 by Sandström.[124] During the next two decades scattered tumors were reported, usually from postmortem examinations. Although the association of these tumors with the clinical syndrome of von Recklinghausen's osteitis fibrosa generalisata had long been recognized, the cure of the disease following the surgical removal of an enlarged parathyroid gland by Mandl in 1925 [93] stimulated greatly increased interest in hyperparathyroidism. The rapidly growing list of case reports, numbering 160 at the time of writing, has added greatly to our knowledge of the condition. No one investigator, however, has hitherto had the opportunity to study more than a few cases, the largest series and the best histological studies to date emanating from Bergstrand with 6 cases,[20-24] and from Hunter and Turnbull with 5.[79, 80] The recognition by Albright and co-workers [3, 5] that systematic studies of the calcium and phosphorus metabolism in all cases of renal stones would unearth a significant proportion of cases of hyperparathyroidism, added to the already keen interest in the clinical syndrome dating from the work of Albright, Aub, Bauer and

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co-workers, [4, 6, 16, 118] Hannon *et al.*, [68, 97] has provided us with 25 cases for study. Within this group we have been able to find examples of nearly every type of the disease recorded in the literature, so that an effort at classification seems justified.

For purposes of orientation, since the classification, and still more the nomenclature, of the types of parathyroid cells is regrettably confused, a study of the normal glands seemed necessary. Although it provides little that can be considered new, we feel that our description of the normal will provide the reader with a base line from which he can more adequately evaluate our descriptions of the diseased glands. We therefore include it in brief form.

The Normal Parathyroid Gland

In 1898 Welsh,[153] after examining the parathyroid glands from 40 human autopsies, published an accurate description of the histology of the normal gland, to which little of fundamental importance has been added. He recognized for the first time the "oxyphil" cell, which he distinguished clearly from the predominant "principal" or "chief" cell. The latter he separated into four subtypes, basing his classification partly on the morphology but more on their arrangement. He believed that the least specialized cell was what is now called the "water-clear" or "wasserhelle" cell, and that as the cell became more specialized it reached the stage of a true chief cell. The arrangement of both the oxyphil and chief cells varied from large continuous masses to anastomosing and then branching columns, and finally to cords a single cell wide. True acini were occasionally, but rarely, found and when present often contained colloid-like secretion.

During the past thirty years many anatomists have studied the normal histology of the parathyroid gland, describing various types of cells. One difficulty in comprehending this normal histology is the nomenclature. Von Verebély [147] describes chief, vacuolated, small and large oxyphil cells; Getzowa,[56] wasserhelle, rosarote and oxyphil cells; Hunter and Turnbull,[80] principal and pale and dark oxyphil cells; Erdheim,[50] a large pale and a dark oxyphil cell; Kurokawa,[85] clear and dark chief cells. This variation suggests that the cell types are not clearly differentiated and that transition forms are numerous.

In 1903 Erdheim [50] showed the presence of fat granules in the chief cells as well as in the stroma. Very little was seen in the oxyphil cells. The fat was not present at birth and began to appear after the third decade, gradually increasing with age. He emphasized the fact that the fat content was not dependent upon the nutrition of the individual, but only upon age.

Kurokawa [85] studied a larger series of about 815 glands removed from 240 autopsy cases at Keio University Medical College. His material ranged from a 7 month fetus to individuals 80 years of age and presents the most adequate survey yet available of the physiological limits of variation. His findings show that up to the age of puberty the cells are all clear chief cells containing glycogen but no fat. At this point these cells begin to decrease and the dark chief and oxyphil cells gradually appear. The dark chief cells contain fat but no glycogen. The oxyphils contain neither fat nor glycogen. Follicles and colloid appear at this time. The oxyphil cells increase with advancing age, occurring in masses and nodules after the age of 30 or 40 years. He found that after puberty there was no tendency for the interstitial connective or fatty tissues to increase, nor was there any atrophy of the gland.

In our study the parathyroid glands were removed from 150 routine autopsied cases. In the majority of these, four glands were found in their normal positions, though in occasional cases only three or even two could be demonstrated. In rare instances supernumerary and aberrant glands have been reported. Parathyroid tissue has been found in the thyroid, thymus, and in other regions of the anterior mediastinum.[28, 99] The glands in each case are usually the same size, though minor variations are not rare. On the average they measure 3–6 mm. in length, 2–4 mm. in width, and 0.5–2 mm. in thickness. They are usually embedded in fat tissue, from which they can be distinguished by their color, which varies from a dark reddish brown to a light tan.

Our material was for the most part fixed in Zenker's fluid, embedded in paraffin, cut at about 8 microns thickness, and stained with eosin and methylene blue. In numerous instances paraffin sections of formalin-fixed material stained with hematoxylin and eosin were also studied. Variations in fixation and staining technique were often found to alter the appearances of the cells significantly. The fat content was determined from frozen sections fixed in 10 per cent

formalin and stained in scharlach R. Preparations of alcohol-fixed material stained for glycogen with Best's carmine were made in about one-half of the cases. It was found that in all but a few cases the various glands from the same individual were practically identical in appearance. We have elected to recognize four major cell types and have been forced to admit the existence of transition types.

The normal chief or principal cell (Fig. 6) is polyhedral in shape, poorly outlined and measures 6–8 microns in diameter. Its nucleus is large, round, sharply demarcated by a basophilic outline, comprises more than half of the cell volume and measures 4–5 microns in diameter. The chromatin is usually abundant, often giving the nucleus a pyknotic appearance. The cytoplasm is usually very scant and faintly acidophilic. Often it is more or less retracted toward the cell margins, leaving an unstained halo of varying width about the nucleus. This is often spoken of as vacuolization, though it may represent merely an artefact of fixation and dehydration. Formalin fixation tends to exaggerate this appearance, and in frozen sections of unfixed tissue vacuolization is difficult to demonstrate even when paraffin sections show it in marked form. Cells showing this halo formation in moderate degree we have termed transition wasserhelle cells.

When the cytoplasm is apparently entirely absent, complete vacuolization, the cell is called a "water-clear" or "wasserhelle" cell. At this stage the cell is sharply outlined and is larger than the chief cell, measuring 10–15 microns in diameter. Its nucleus is about the same size as that of the chief cell, but is usually more hyperchromatic, more often pyknotic, and eccentrically located. These cells are seen only occasionally in the apparently normal gland and then in small groups. We have not observed them before puberty. Their presence in small clusters has sometimes been interpreted as focal hyperplasia. When the whole gland is composed of these cells, as in some cases of nephritis and hypertension, it is felt that hyperplasia is definite.

The pale oxyphil cell (Fig. 7) is polyhedral in shape, has a sharply demarcated cell margin and measures 11–14 microns in diameter. The nucleus is also about the same size as that of the chief cell, but not so hyperchromatic. The cytoplasm is uniformly reddish pink, finely granular and completely fills the cell. There is no vacuolization.

The dark oxyphil cell is larger than the chief cell but smaller than the pale oxyphil, and measures 8–10 microns in diameter. Its cell border is not sharp. The nucleus is small, 3–4 microns, and intensely pyknotic. The cytoplasm is dark red and homogeneous.

The distribution of these cells varies with age. Until puberty the gland is composed wholly of chief cells with a slight tendency to vacuolization (Fig. 1). We cannot subscribe to Kurokawa's[85] classification of them as wasserhelle cells. These cells contain a fair amount of glycogen but no fat, the latter appearing soon after puberty as very fine droplets. At puberty or soon afterward pale oxyphils gradually appear, at first singly and then in pairs. They increase in number with advancing age, forming large islands usually after 40 to 50 years of age (Fig. 3). These islands are sharply circumscribed but not encapsulated, and often continuous cords of parenchymal cells can be traced across the margin into the surrounding tissue. These cells do not contain fat or glycogen. Dark oxyphil cells occur singly and usually close to the stroma. They are not present before puberty, and occur usually when pale oxyphils are present. They likewise do not contain fat or glycogen.

Following puberty large fat cells appear in the stroma and increase in number until about 40 years of age (Fig. 2). The fat tissue remains fairly constant during middle age and does not increase with old age. In fact, in cases where the individual was over 80 years of age, in which oxyphil groups are numerous, it is somewhat diminished. It is interesting to note that when an adult gland is smaller than normal the decreased size is due to the absence or marked diminution of fat cells, whereas the parenchymal cell volume is about the same as in a normal sized fat-containing gland. These observations on the fat content do not wholly coincide with those of Erdheim.[50]

Cysts of varying sizes are observed in about one-half of the cases beyond puberty (Fig. 4). In 2 cases one of the glands was composed almost wholly of one large cyst similar to that described by Alagna.[2] These cysts are filled with granular and cellular débris or with a dark blue-staining, finely granular material which is often, though perhaps improperly, termed colloid.

In one case a small, circumscribed, apparently non-functioning adenoma 3–4 mm. in diameter with a distinct fibrous capsule was found in one of the glands. The cells of this tumor were classified as a transition stage between chief and pale oxyphil cells (Fig. 5).

Cases of Hyperparathyroidism

The clinical and surgical aspects of many of these cases have already been reported elsewhere in detail and reference to them will be given with each description. Cases 1–17 are collected in a paper by Albright, Aub and Bauer.[4] The surgical features in the treatment of these cases have been reported by Churchill and Cope.[32, 33] The case numbers in the present series have been kept identical with those of the clinical studies.

With the gradual accumulation of material it became evident that one fundamental line of division could be drawn. One group of cases, the smaller one, was characterized by a diffuse, uniform alteration of all the parathyroid tissue in the body (Figs. 8–13). In the second group one gland, often only a part of it, rarely parts of two glands, were abnormal (Figs. 15–26), whereas the remaining parathyroid tissue was grossly and microscopically within the limits of normal variation. That the first group is to be regarded as hyperplastic, dependent on some external chemical, hormonal or nervous stimulation, seems obvious. That the second group falls within the accepted limits of neoplasia is a thesis we shall attempt to defend. The case reports which follow have been grouped according to this general classification and then further subdivided on purely morphological grounds of similarity of cell type and structure.

Group A: Hyperplasia

Case 15 [8, 4, 32] (33–4840 and 34–796). *Clinical History:* A. P., a widow, 62 years of age, was first admitted in 1928 because of bilateral renal calculi. At this time two stones were removed from the right kidney pelvis, but in November, 1933, bilateral renal calculi were again found. The non-protein nitrogen was 32 mg. and the phenolsulphonephthalein excretion was only slightly impaired. The urine contained many white blood cells. A stone was removed from the left ureter. Serum calcium was 15 mg., phosphorus 2.2 mg., phosphatase 7.3 Bodansky units. X-rays of the skeleton were negative. On Dec. 19, 1933, at operation a parathyroid tumor was demonstrated below the right lobe of the thyroid and another on the left in a symmetrical position. Both were removed and the dissection was carried no further. Postoperatively the serum calcium at first fell, but soon began to rise. On Dec. 26, 1933, the serum calcium was 15.4 mg., the phosphorus 2.2 mg. On Feb. 28, 1934, a second operation was performed at which the left upper parathyroid was not demonstrated, but the right upper was found greatly enlarged and was resected, a portion about twice the size of a normal gland being left in place. In April, 1934, the serum calcium was 11.4 mg., the phosphorus 2.2 mg. When last seen, on June 30, 1934, the serum calcium was 13.78 mg., the phosphorus 2.75 mg.

Gross Description: The specimen removed from the region of the lower pole of the right lobe of the thyroid weighs 0.61 gm. and measures 1.5 by 1.2 by 0.5 cm. The gland is encapsulated, smooth surfaced and deep reddish brown in color. On one surface there is a curved shallow depression. The cut surface is homogeneously reddish brown. The specimen removed from the region of the lower pole of the left lobe of the thyroid weighs 0.51 gm. and measures 1.8 by 0.8 by 0.6 cm. It is slightly paler but otherwise the same as the other specimen.

The specimen removed 71 days later (34–786) from the region of the upper pole of the right lobe of the thyroid weighs approximately 10 gm. and measures 5 by 3 by 1.3 cm. Its surface is reddish brown, smooth and glistening, except where several small clear cysts averaging 0.5 cm. in diameter project from it. On section the surfaces are reddish brown, with cysts which yield a little clear straw-colored fluid.

Microscopic Examination: Both specimens removed at the first operation have the same microscopic appearance. The capsule is thin and no normal parathyroid tissue is found within or outside of it.

There is only one type of cell throughout, the wasserhelle cell (Fig. 9), which is polyhedral in shape, sharply demarcated by a thin eosinophilic membrane, and varies from 10 to 40 microns in diameter, averaging 15 to 20. Many of the cell boundaries are broken, with resultant fusion, similar to the fusion of alveoli in pulmonary emphysema. In contrast to the variability in the size of the cells the nuclei, though often multiple, are all approximately the same size, averaging about 8 microns in diameter. They are round to slightly ovoid in shape, sharply outlined, moderately hyperchromatic, with an eccentrically placed nucleolus. As a rule the nuclei are located in the end of the cell that is contiguous to the stroma. This produces a characteristic pattern which resembles branches of berries (Fig. 11). The cytoplasm is clear except for a little, light pink-staining granular material. Many of these tiny granules are glycogen deposits. Similar granules are present within the nuclei. There is no fat, except for a rare droplet in the stroma. The low power appearance of the histological sections is so similar to that of clear cell renal carcinomas that distinction would be difficult if the source were not known. In fact one gland of this type was actually reported as a hypernephroma of the thyroid.[84]

The stroma is composed of thin, fibrous connective tissue bands containing a moderate number of connective tissue cells and relatively few blood vessels. These bands surround small and large groups of cells, producing a pseudoglandular effect. This effect is further emphasized by the position of the nuclei, as mentioned above. Occasionally a true single layered alveolus is seen. No oxyphil or chief cells are found. There are no mitoses.

The cells in the specimen removed at the second operation are of the same type as those present in the other two glands. The same characteristic pattern is produced by the peripheral location of the nuclei, but there is more marked gland and cyst formation. These spaces vary in size from 0.1 to 5 mm. They are usually lined with a single layer of wasserhelle cells. Their lumina are filled with pink-staining granular débris and at times with desquamated lining cells and red blood cells (Figs. 8 and 9).

CASE 16[5, 4, 32] (34–634). *Clinical History:* T. F., a male, 26 years of age, entered on the urological service because of intermittent attacks of right renal colic for 15 months. Physical examination was negative. The non-protein nitrogen was normal. Serum calcium was 15.1 mg., phosphorus 1.8 mg. The urine showed finely granular casts of the hyperparathyroidism type (containing calcium phosphate).[7] X-rays of the skeleton were negative, but films of the urinary tract showed two small stones in the right ureter. These were removed and later, on Feb. 16, 1934, a parathyroid tumor below the right lower pole of the thyroid at the sternoclavicular junction was resected. Directly beneath this lay a second, much larger tumor, which came from the surface of the prevertebral fascia and the posterolateral aspect of the trachea and esophagus. This was also excised. The following day the serum calcium was 11.9, the phosphorus 2.6 mg. When last seen, on April 13, 1934, the serum calcium was 10.2, the phosphorus 2.3 mg.

Gross Description: The first gland is a well circumscribed, encapsulated, smooth surfaced, orange-brown ovoid mass weighing approximately 0.6 gm. and measuring 1.5 by 1 by 0.6 cm. The cut surface is uniformly yellowish brown.

The second gland is an encapsulated, smooth surfaced, ovoid soft tumor weighing approximately 15 gm. and measuring roughly 4.5 by 3.5 by 2.5 cm. Both poles are slightly pointed and narrowed. The surface is reddish brown. At one pole there is a small cyst 0.8 cm. in diameter filled with clear colorless fluid. The cut surface is homogeneously yellowish to reddish brown, soft and glistening.

Microscopic Examination: The microscopic picture of both of these tumors is identical. They are completely made up of large wasser-

helle cells of the same type as that seen in Case 15. There are no chief or oxyphil cells. No normal parathyroid tissue is present.

The cells in this case, as in Case 15, are in many places arranged in true gland formation. The characteristic pattern produced by the peripherally placed nuclei is much more pronounced than in Case 15 (Figs. 10 and 11).

CASE 17 [8, 4, 32] (34–600). *Clinical History:* J. M. M., a female, 55 years of age, entered on the urological service for intermittent attacks of renal colic for the past 14 months. Physical examination was negative. A stone demonstrated by X-ray in the right ureter was removed. The non-protein nitrogen was 31 mg. Serum calcium was 12.7 mg., phosphorus 2.4 mg., phosphatase 4.2 Bodansky units (normal). X-rays of the skeleton were negative. At operation on Feb. 14, 1934, all four glands were found in normal position and were enlarged. Three, and a portion of the fourth were removed. The following day the serum calcium was 10.9 mg., the phosphorus 2.2 mg. When last seen, on June 25, 1934, the serum calcium was 10.34 mg., the phosphorus 2.99 mg.

Gross Description: (*Left Upper*): A soft, reddish brown, slightly nodular, irregular, non-granular piece of tissue weighing 2 gm. and measuring approximately 2 by 2 by 1 cm. The specimen has been cut in several places. (At operation the recurrent laryngeal nerve had to be dissected free.)

(*Left Lower*): Weighs 0.6 gm., measures 1 by 0.8 by 0.4 cm.

(*Right Upper*): A small biopsy approximately 1 mm. in diameter.

(*Right Lower*): Weighs 0.8 gm., measures 1.8 by 1.2 by 0.4 cm.

The cut surface of all the specimens is homogeneously reddish brown.

Microscopic Examination: The microscopic picture of all sections is identical with Cases 15 and 16.

CASE 23 (34–2729). *Clinical History:* A. S., a male, 41 years of age. In August, 1932, the patient passed a renal stone. Three months later his physician removed three stones with the aid of a cystoscope. One month later he complained of a tight feeling in the left hip, soon followed by soreness in the hypogastrium and left lower quadrant. Cystoscopy was negative. He lost 35 pounds in weight. At the Massachusetts General Hospital in Feb., 1934, X-rays showed a cystic tumor of the left ilium and calcification in the lower pole of the left kidney. The bone lesion was resected and was diagnosed as an atypical chondrosarcoma. No changes in the least suggestive of osteitis fibrosa cystica were demonstrated. Examination of the urine showed a slight trace of albumin, 20–60 white blood cells, and occasional red blood cells. Bence-Jones protein was found on one occasion. The serum calcium was 13.1 mg., serum phosphorus 2.92 mg. After discharge the patient felt somewhat better for a while but soon the abdominal symptoms returned and he reentered for parathyroidectomy. The laboratory findings were essentially the same. On July 11, 1934, operation was performed.

The left upper, left lower, and right lower parathyroid glands were found enlarged and removed. A small biopsy was taken from an apparently normal sized right upper. Postoperatively the serum calcium went down slowly, reaching 10.18 mg. on the 10th day; the phosphorus was 3.4 mg. Three months later the corresponding figures were 11.96 mg. and 3.69 mg.

Gross Description: (*Right Lower*): a reddish brown, slightly flattened, smooth surfaced soft mass weighing 0.13 gm. and measuring 8 by 6 by 3 mm.

(*Right Upper*): A small biopsy 1 mm. in diameter.

(*Left Upper*): A multilobulated, reddish to yellowish brown, irregularly shaped, smooth surfaced mass weighing 2.18 gm. and measuring approximately 3 by 1.7 by 0.8 cm. The largest lobule measures 3 by 1 by 0.8 cm. and is more yellow than the rest of the specimen.

(*Left Lower*): A deep reddish brown, ovoid soft mass weighing 0.16 gm. and measuring 1.1 by 0.6 by 0.3 cm. The cut surfaces of all the specimens are homogeneously reddish brown.

Microscopic Examination: The cells are all of the large wasserhelle type, arranged in gland formation and showing the typical pattern seen in Cases 15, 16 and 17.

CASE 25 (34–4318). *Clinical History:* W. P., a male, 39 years of age, began in August, 1934, to have attacks of sharp pain in the right flank. The pain occurred suddenly at any time of the day or night and lasted 2 to 3 minutes. On October 1st he was awakened at night by an attack which persisted for several hours and which was finally relieved by morphia. During a 3 day period of observation at a local hospital he had three more similar attacks, all requiring morphia for relief. On Oct. 4, 1934, he was admitted to the Massachusetts General Hospital where a stone, demonstrated by a pyelogram, was removed from the right ureter. X-rays of the skeleton were negative. The serum calcium was 13.91 mg. per 100 cc., serum phosphorus 2.96, and phosphatase 3.67 units. At operation on October 27th the right upper parathyroid was found enlarged. A rush frozen section of a biopsy of this gland showed large wasserhelle cells typical of hyperplasia.* With this information the surgeon continued his search for the other glands and exposed all four. Both uppers were markedly enlarged and were resected. The lowers were much smaller. One of them was completely removed and three-quarters of the other was resected. On October 29th the serum calcium was 9.43 mg. per cent, serum phosphorus 1.34. There were no signs of tetany. The patient was discharged on Nov. 5, 1934.

Gross Description: (*Right Upper*): An irregular, slightly lobulated tumor weighing 4.96 gm. and measuring approximately 3.7 by 2 by

* In order to bring out the marked vacuolization of these wasserhelle cells it is advisable before freezing to fix the tissue by heating it to the boiling point in 10 per cent formalin.

1 cm. At one pole there is a long pseudopod-like projection 5 mm. in length and 3 mm. in diameter.

(*Left Upper*): Weighs 1.63 gm. and measures 1.7 by 1.7 by 0.6 cm. with a pseudopod-like tab 5 mm. in diameter.

(*Left Lower*): Weighs 0.11 gm. and measures roughly 4 mm. in diameter.

(*Right Lower*): Two small pieces weighing 0.10 gm.

The surfaces of all the specimens are smooth and reddish to yellowish brown. The cut surfaces are homogeneously pink to yellowish gray, moist and translucent.

Microscopic Examination: The microscopic picture of all sections is identical with Cases 15, 16, 17 and 23. A piece of thyroid removed at operation was histologically normal.

Summary of Cases 15, 16, 17, 23 and 25 (Wassershelle, Generalized)

The similarity of these 5 cases is at once apparent from an examination of the sections. The uniform, unusually large clear cells, the tendency to acinar arrangement and the basal orientation of the nuclei present a uniformity of appearance that is entirely lacking in the group of localized tumors to be described below. It differs also from the hyperplasia produced experimentally in rabbits by the injection of an extract of the anterior pituitary. In these experiments Hertz and Kranes [74] found enlarged chief cells with comparatively slight vacuolization and numerous mitoses.

The similarity to the clear cell renal adenocarcinoma is striking and in fact, as already reported in the text, has misled previous observers.[84]

In Cases 17, 23 and 25, histological specimens were obtained from all four glands and diffuse involvement of all the parathyroid tissue proved beyond doubt. In Case 15 only three glands could be demonstrated in two extremely thorough operative dissections. In Case 16 only two enlarged glands were demonstrated, but no search was made for the other glands at the time of operation and the patient has not returned to the clinic. However, the histological similarity to the other cases makes us feel that it should be classified with this group.

CASE 23A* (7119). *Clinical History:* R. N., a female, 25 years of age, entered the Maine General Hospital in April, 1933, complaining of weakness and fatigue. She had had polyuria and polydipsia all her life, with no recent change. Her teeth had all been loose for 7 years. She had had pain, weakness and numbness of the legs for the past 8 months. Examination showed a small mass 8 by 4 mm. in the middle of the right neck. The blood pressure was 158/78. Examination of the urine showed a fixed specific gravity around 1.005, 40–60 mg. of albumin, and 10–20 white blood cells. Examination of the blood showed a red cell count of 1,980,000, with a hemoglobin of 35 per cent. The white blood cell count was normal. The non-protein nitrogen of the blood was 150 mg. On her second admission in September, 1933, the laboratory examinations were about the same. X-rays of the skull, ribs and hands showed definite cysts, as well as calcification of the arteries and subcutaneous tissues. The serum calcium was 8 mg., serum phosphorus 9 mg. Although these blood studies appear paradoxical, they may be explained according to Albright by the marked renal damage. The phosphate retention secondarily causes a diminution in blood calcium. The patient died Nov. 6, 1933. Postmortem examination showed in addition to the parathyroid enlargement a marked chronic pyelonephritis and osteitis fibrosa. A clinical diagnosis of renal rickets could not be ruled out.

Gross Description: All the parathyroid glands except the right lower are enlarged. The left lower is ovoid in shape and measures 9 by 7 by 3 mm. The left upper is the largest and measures 17 by 8 by 5 mm. It contains on its posterior surface a circular nodular elevation 3 mm. in diameter. The right upper measures 10 by 8 by 4 mm. The glands are smooth surfaced, and in spite of having been previously fixed in formalin still retain a slight yellowish brown tint.

Microscopic Examination: All the glands, including the normal sized one, show essentially the same process in varying degrees, the most marked changes being in the largest gland. The capsules are thin and not remarkable. The predominating cell is the chief cell, which is normal in size, averaging 8 microns in diameter. The cell outline is poorly visualized. The nucleus is round, deeply pyknotic and hyperchromatic, sharply outlined, measures 5–6 microns in diameter, and fills more than two-thirds of the cell volume. The cytoplasm is acidophilic and coarsely granular. The cells themselves are, therefore, not hypertrophied.

The arrangement of the cells presents the most significant picture.

* In addition to the 24 surgical cases included in this study, we have had the opportunity to study the parathyroid glands removed at autopsy from a case at the Maine General Hospital. The findings are quite different from any of our own cases. The authors wish to thank Drs. John Hamel and Mortimer Warren for permission to report the pathology of this case.

In order not to break the series of cases from the Massachusetts General Hospital, this case is numbered 23A instead of 24.

Small groups of these cells, 10–20 in number, are surrounded by a thin connective tissue band often containing a very small capillary. The nuclei tend to be located at the bases of the cells and produce a definite pseudoglandular arrangement, although there is no lumen. Each group appears to be shrunken away from its connective tissue band, leaving a clear space about 6–9 microns in width. In many places, especially in the larger glands, acinar arrangement is much more marked, forming well circumscribed, papillary foci measuring up to 0.8 mm. in diameter (Figs. 12 and 13). These resemble closely the basophilism frequently observed in the pituitary. There is very little inter- or intracellular fat tissue.

Scattered throughout all sections, but more marked in the larger glands, are groups of typical, normal sized, pale oxyphil cells arranged in the same formation as the chief cells, even including the papillary form. There are no wasserhelle cells.

Summary of Case 23A (Hyperplasia, Chief Cell Type)

This patient showed three enlarged and one normal sized parathyroid gland all made up of normal sized chief and pale oxyphil cells arranged in pseudoglandular and papillary formations. There is very little fat tissue and no wasserhelle cells.

Group B: Neoplasia

Case 6 [118, 68, 16, 97, 6, 5] (32–3985). *Clinical History:* C. M., a male, 35 years of age. The clinical history of Captain Martel has appeared so often in the literature that no attempt will be made to repeat it. The diagnosis made by Dr. Eugene DuBois in 1926 was the first clinical recognition of hyperparathyroidism in this country, and probably the second in the world. The coöperative attitude of the Captain made possible a series of metabolic studies that are unparalleled and have contributed enormously to our knowledge of the disease.

Operation was performed first by Dr. E. P. Richardson in 1926, and two normal parathyroid bodies were removed. An article describing the case has been widely misquoted as recording improvement following this operation, but any such tendency was temporary and may more fairly be attributed to the high calcium diet. As the disease progressed the renal damage became more marked and stones formed in the kidney pelves. The serum calcium averaged 15 mg., phosphorus 2.3 mg. At the seventh operation, by splitting the sternum a parathyroid tumor was found in the anterior mediastinum. Subtotal resection was performed. Severe tetany supervened, which was controlled with difficulty, owing to acidosis attributable to the renal damage. Six weeks after the removal of the parathyroid tumor a stone was passed into the left ureter, causing complete obstruction. With the patient in a dangerous balance between tetany and aci-

dosis and in the face of a markedly diminished renal function, a left ureterolithotomy was undertaken. Death occurred 26 hours later. Postmortem examination showed well marked osteitis fibrosa cystica with early evidence of healing, and marked renal calcinosis.

Gross Description: A smooth, round, hard nodule 2.5 cm. in diameter. On cutting through the nodule it is seen to have a calcified shell 1–2 mm. in thickness, the rest of the tumor being made up of soft, shiny, brownish material. The tumor has a soft fibrous pedicle.

Microscopic Examination: The tumor is made up of only one type of cell, the chief cell (Fig. 17), which measures about 8–11 microns and has a poorly demarcated, pinkish, polyhedral cell outline. The nucleus is large, filling about one-half of the cell body, is round, sharply demarcated, and contains a variable amount of chromatin. Many of the nuclei, especially of the smaller cells, are deeply basophilic and almost pyknotic. The cytoplasm is light pink, coarsely granular and in many places reticular. A large proportion of the cells has a vacuolated halo around the nucleus and in a few the vacuolation extends to the periphery. An occasional cell is multinucleated; there are no mitoses. The cells contain no fat. There are no typical wasserhelle or pale oxyphil cells and only an occasional dark oxyphil cell.

The cells are arranged in compact masses, columns, and in pseudoglands, though one section shows a few definite acini lined with chief cells and filled with pink-staining, homogeneous material. The vessels of the intervening stroma are more numerous, much larger and much more congested than those in the normal parathyroid. Scattered throughout the stroma are variable sized spaces without demonstrable lining measuring up to 1 mm. in diameter. Many of these are empty, but others contain colloid-like, pink-staining material or red blood cells, and occasionally a desquamated parathyroid cell. There are also small colloid droplets throughout the stroma.

CASE 7 (32–4132). *Clinical History:* M. R., a female, 36 years of age. In 1929 the patient developed dull pain in her arms and legs. In 1931, at another hospital where her bones were found to be decalcified and filled with cysts, a diagnosis of osteitis fibrosa cystica was made. Serum calcium was 14.1 mg., phosphorus 2.9 mg. On Oct. 19, 1931, a tumor, supposedly of parathyroid origin, was excised, but microscopic examination revealed thyroid tissue. A biopsy of the mandible, 6 months later, showed osteitis fibrosa cystica. On May 6, 1932, a right hemithyroidectomy was done and a tumor at the left lower pole was removed. Microscopic examination revealed thyroid and thymic tissue. In November, 1932, she

entered the Massachusetts General Hospital for the first time. The serum calcium was 12 mg., phosphorus 1.74 mg., phosphatase 16.9 units. X-ray confirmed marked decalcification and multiple fractures in the pubic bones. She had paralysis of the right vocal cord. On Nov. 15, 1932, after fruitless exploration of the neck, a tumor was found in the anterior mediastinum beneath the costal cartilage of the second rib at the border of the sternum. A subtotal resection was done. During convalescence the patient developed definite tetany, associated with a fall in serum calcium. On Nov. 29, 1932, the serum calcium was 5.16 mg., phosphorus 3.29 mg. When last seen, on May 17, 1934, the bones showed great improvement. The serum calcium was 8.39 mg., phosphorus 3.03 mg. The phosphatase was 5.08 units.

Gross Description: A pedunculated, brownish, lobulated, firm encapsulated tumor measuring 2.5 by 3 by 1 cm. The cut surface is brown and shows many firm lobules varying in size from 3–6 mm. in diameter.

Microscopic Examination: About the same as in the preceding case. Palisading of cells is very prominent. In many places the columns are so winding and the intervening vascular stroma so abundant that there is almost a papillary arrangement. Scattered throughout the stroma are numerous large mast cells.

CASE 9 (33–1226). *Clinical History:* J. R. C., a male, 33 years of age. In 1931 the patient gradually developed weakness, loss of weight, nocturia and pains in the legs noticeable when walking. In 1932 the pain in the legs was almost constant when upright. He became much weaker, lost 30 pounds in weight, and by January, 1933, was unable to work. A diagnosis of hyperparathyroidism was made at the Boston Dispensary, where X-rays were taken of his bones and calcification of the kidneys observed. A history of mild polyuria and polydipsia was elicited. In March, 1933, he entered the Massachusetts General Hospital, where X-rays showed marked generalized decalcification of the skeleton with cyst formation. There was a markedly depressed renal function, a low urine specific gravity and a secondary anemia. The serum calcium was 16.9 mg., serum phosphorus 3.02 mg. On April 4, 1933, at operation a tumor lateral and posterior to the lower portion of the left lobe of the thyroid was resected. The dissection was limited to the left side of the neck. Convalescence was characterized by prolonged and severe tetany. When last seen, on July 24, 1933, steady improvement in appetite and strength was noted. He had gained 30 pounds in weight, had much less pain on walking and less nocturia. The anemia had improved moderately although the renal function was the same. Calcium and phosphorus values were normal, but phosphatase was slightly elevated. X-rays showed no change in skeleton or kidneys.

Gross Description: An ovoid, yellowish pink, soft, encapsulated mass measuring 4 by 2.2 by 2 cm. and weighing 7 gm. The cut surface is soft, friable, mushy and yellowish gray.

Microscopic Examination: The capsule is slightly thick, in places

measuring almost 1 mm. It is composed of fibrous connective tissue with only a few cellular areas. One of these areas is close to the inner surface of the capsule and contains lymphocytes, red cells and deposits of hemosiderin.

The cells in this case are larger than those of the preceding 2 cases, measuring 11 to 14 microns in diameter. The nuclei measure 8–10 microns and are hyperchromatic, but no definite multinucleated cells or mitotic figures are seen.

Summary of Cases 6, 7 and 9 (Chief Cell Type Alone)

These 3 cases are all composed of large, hyperchromatic chief cells arranged in pseudoglandular and columnar formation (Fig. 17). Cases 7 and 9 show well marked palisading. Neither the cells nor the stroma, which is vascular, contain any fat. There are no wasserhelle or pale oxyphil cells, and only an occasional dark oxyphil cell. Multinucleated cells are rare and no mitoses can be found.

CASE 1 (30–3056). *Clinical History:* M. J. S., a female, 46 years of age. In 1916, following a miscarriage, the patient noted a swelling in the right side of her neck. Between 1928 and 1930 she developed pain successively in the right arm, right thigh, left thigh and right forearm. A biopsy of the right ulna at the Worcester Memorial Hospital showed a giant cell tumor, for which she was given X-ray therapy. Numbness and pain in the legs increased. She entered the Massachusetts General Hospital where X-rays showed generalized osteitis fibrosa cystica. A secondary anemia was present. Serum calcium was 13.68 mg., phosphorus 2.58 mg. At operation a tumor was seen pushing the right lobe of the thyroid forward. Hemithyroidectomy with total resection of the tumor was performed. After 2 months the pains had diminished and appetite, strength and gait had improved, though anemia was still present. Calcium and phosphorus levels were normal. By the 8th postoperative month she had gained 40 pounds, all skeletal pain had ceased and constipation had disappeared. Her strength was better than since 1916. X-rays showed slight but definite improvement in the bones. Two and a half years later she felt very well except for occasional backache. The cysts remained unchanged by X-ray. The serum calcium was 9.38 mg., phosphorus 3. 41 mg., phosphatase 2.58 units.

Gross Description: A light brown, ovoid, moderately firm, encapsulated mass, measuring 6.5 by 5 by 3.5 cm., and weighing 53.2 gm. The cut surface is homogeneously pale, glistening and yellow brown.

Microscopic Examination: The major portion of all sections is made up of closely packed cells arranged in pseudoglandular, cord or strand-like columnar formations. The pseudoglandular areas are composed of irregular, rounded groups of cells, from five to fifty in each group. The columnar areas are usually two or three cells in

width, but are comparatively few in number as compared with the pseudo-alveolar.

The predominant cell is polyhedral in shape and varies in size from 5 to 20 microns (Fig. 18). Its cell outline is often indistinct, but in many places can be made out as a thin, slightly irregular pink line. The smaller cells have round and light staining nuclei; the larger, some of which are almost 20 microns in diameter, have large, irregular, and more hyperchromatic nuclei, sometimes reaching the size of four to six ordinary nuclei. Chromatin is abundant and usually a nucleolus can definitely be made out. For the most part the cytoplasm immediately surrounding the nucleus is absent, producing a halo from the periphery of which pinkish granules extend to the cell margins, though a fair proportion of the cells have a pink, finely granular cytoplasm which completely fills them. A small proportion of these cells has one or two small fat granules in its cytoplasm, but the majority of them contain no fat. Multinucleated cells are fairly numerous; some contain as many as seven nuclei. Although no mitoses are seen, the atypicality of the nuclei, as evidenced by the variation in their hyperchromatism and the frequency of multinucleated cells, strongly suggests a neoplastic rather than a hyperplastic process.

Single, dark oxyphil cells are present in small numbers. They are of normal size, about 8–10 microns in diameter, with a dark, deeply basophilic irregular nucleus surrounded by a deeply eosinophilic, finely granular cytoplasm. The nuclei are either small, about one-fifth the cell volume, or large, about three-fourths of the cell volume. These cells lie for the most part close to the interstitial stroma and are not found in groups. No wasserhelle cells are seen.

The stroma is composed of thin fibrous strands which pass around groups of cells, producing pseudo-alveoli or columns. A small proportion of the stroma is acellular, but most of it contains thin-walled capillaries lined by typical endothelial cells. In some areas larger vessels partially filled with blood are seen. There are practically no fat cells in the stroma.

Scattered throughout the tumor are irregularly shaped spaces varying in size from 50 to 200 microns. They have a connective tissue lining, are surrounded by masses of chief cells, and contain for the most part pink-staining, granular débris, occasionally a few red blood cells, but no colloid. Besides these there are also much larger,

irregular confluent spaces without any definite lining, which also contain pink-staining granular débris. These appear to be areas of localized edema of the stroma.

CASE 11 (33–2429 and 33–4429). *Clinical History:* M. T., a female, 53 years of age. From 1920 to 1923 she had pain in the legs and disturbance in gait. In 1929 an operation was performed on a giant cell tumor of the upper jaw. Later a second tumor in the nose was curetted. In 1930 she fractured the left forearm and left tibia by tripping on a rug. Abdominal pain led to an operation for replacement of the uterus. The severe pains in the legs continued and in 1931 a cystic tumor of the right tibia, discovered by X-ray, was curetted, but she remained completely invalided except for limited activity with crutches. In 1933 severe pain in the legs and lower back was associated with a spontaneous fracture of the neck of the right femur and a diagnosis of osteitis fibrosa cystica was made at the Cambridge City Hospital. She was transferred to the Huntington Hospital where the diagnosis was confirmed by Dr. J. C. Aub. X-rays showed extensive decalcification and cyst formation of the entire skeleton and calcium deposits in the kidney parenchyma. Her condition seemed critical, with respiratory distress, nausea and vomiting. The serum calcium was 13.7 mg., serum phosphorus 2.4 mg., the phosphatase elevated. Renal function was diminished. At operation at the Massachusetts General Hospital on June 24, 1933, a subtotal resection of parathyroid tumor found behind the left upper pole was performed. Approximately 1 gm. of parathyroid tissue was left. A nodular goiter was noted. A mild tetany developed, the calcium falling as low as 7.4 mg. A second fracture of the femur occurred when the traction apparatus was changed. In September, 1933, she was comfortable but the bones showed no evidence of increased density and the fractures failed to develop callus. The extreme decalcification of the skeleton was treated with a high calcium diet, vitamin C, viosterol and calcium glycerophosphate. The serum calcium rose to 11.53, the phosphorus was 3 mg. On Nov. 15, 1933, a second operation was done, with excision of the remainder of the parathyroid tumor. One week later the calcium was 8.47 mg., the phosphorus 3.12 mg. When last seen, on March 17, 1934, locomotion was much improved, and the fracture seemed solid.

Gross Description: A partially encapsulated, smooth brown nodule measuring 3 by 2 by 1 cm. and weighing 3.85 gm. Many vesicles are present on the surface. On section the center of the tumor is found to be composed of a calcified area roughly 5 mm. in diameter. The tumor tissue is homogeneously brown and firm.

A second piece of similar tissue measuring 2.1 by 1.1 by 0.8 cm. and weighing 1.2 gm. is also present.

Microscopic Examination: The capsule is moderately thickened and composed predominantly of acellular fibrous connective tissue. In a few areas there are some connective tissue cells and clumps of lymphocytes. The subcapsular vessels are markedly distended and congested.

This tumor contains three types of cells. The one that makes up the bulk of the tumor is the enlarged chief cell, similar to that seen in the group just described (Cases 6, 7 and 9). In sharp contrast to these cells there are intermingled with them large numbers of cells apparently in the same class as the chief cell, but tremendously enlarged, much more hyperchromatic, and similar to the giant type of cell described in the previous case. Under low power each field appears to be irregularly studded with them. These cells lie side by side and make up about one-third of the whole mass. They vary greatly in size, the smaller ones averaging 14–17 microns in diameter, the larger about 20 microns; many reach as high as 30 microns (Fig. 18).

The third type of cell in this specimen is similar to the slightly enlarged chief cell, except that its cytoplasm is homogeneously much more eosinophilic. These cells are arranged in large clumps and located only at the periphery. They are not the characteristic pale oxyphil cells but are merely a slight variation from the normal chief cell. No true pale oxyphil cells are seen.

The whole tumor has a well marked pseudoglandular arrangement. Although most of this formation is produced by columns and masses of cells surrounding and bordering capillaries and larger blood vessels, a large proportion is formed around unclassifiable spaces, many of which are filled with granular, blue-staining débris. In many places the cells bordering these spaces or blood vessels show definite palisading. Here the nuclei are located at the pole of the cell, away from the apparent glandular lumen. In places where only a single layer of cells surrounds a small capillary the nuclei are also at the pole of the cell, more distant from the capillary lumen. All types of cells share in this arrangement, although there is a tendency for the smaller ones to border the pseudogland or space.

The stroma consists of scanty strands of fibrous connective tissue, a small amount of fat, and vessels which are increased in number but not remarkably congested. No colloid is seen.

The remainder of the tumor (33–4429), removed at the second operation, is an irregular, orange-gray piece of tissue measuring 6 by 4 by 3 mm. Microscopically it is similar to the specimen removed at the subtotal resection. There is a large amount of scar tissue containing many foreign body giant cells distributed around and throughout the specimen, undoubtedly due to the trauma of the previous operation. The same three types of cells are found. The only

possible difference between the two specimens is the relatively increased vesiculation of the chief cells. The latter, however, have not reached the stage in which they can be called true wasserhelle cells.

An interesting incidental finding was the removal of a small piece of pinkish gray tissue measuring 1.5 by 0.7 by 0.4 cm., containing a small cyst-like structure 4–5 cm. in diameter. At operation this specimen, which was in the same field, was believed to be parathyroid. Microscopically it is a papillary cystadenoma, possibly carcinoma, probably arising in aberrant thyroid tissue.

Summary of Cases 1 and 11 (Chief Cell Type with Giant Forms)

The 2 cases in this group are similar to those in the first group (Fig. 18). They have in addition large numbers of giant forms of exceptionally hyperchromatic chief cells measuring up to 30 microns in diameter, many of which are multinucleated. There are no wasserhelle or pale oxyphil cells. The histological picture is strong presumptive evidence for a neoplastic condition.

CASE 3[5] (32–1304). *Clinical History:* C. S., a female, 13 years of age. In 1928 nocturia with enuresis and polyuria developed. She had always drunk large amounts of water. That same year she fractured the right forearm in two places following an injury of considerable violence. In 1930 a limp, at first attributed to fallen arches, was followed in 6 months by the appearance of a deformity of the left knee. This led to the removal of a cyst from the lower end of the femur, and in 1931 a similar deformity of the right knee developed. In March, 1932, X-rays of the skull, pelvis and vertebrae taken at the Massachusetts General Hospital were characteristic of hyperparathyroidism. Almost complete decalcification of the epiphyses, suggesting renal rickets, was interpreted as failure of calcification of growing cartilage. Serum calcium was 12.5 mg., phosphorus 4.7 mg., phosphatase 36 Bodansky units. Urinary calcium excretion was within normal limits, fecal calcium increased. Renal function was greatly reduced and non-protein nitrogen was elevated. On April 9, 1932, at operation a tumor between the trachea and esophagus on the right side was resected. The serum calcium fell to 10.36 mg. 6 hours later and reached 8.26 mg. in 22 hours, at which time she had moderate tetany. On May 9, 1932, the serum calcium was 5.67 mg., phosphorus 5 mg. When last seen, on May 14, 1933, she felt much stronger but was still subject to fatigue. There was no further polyuria or nocturia. X-ray films showed definite improvement.

Gross Description: A somewhat ovoid, smooth surfaced, moderately firm, light brown mass measuring 22 by 17 by 10 mm. and weighing 2.5 gm. The cut surface shows the same uniform light brown color.

Microscopic Examination: The capsule of the tumor is composed of thick fibrous collagenous connective tissue approximately 45 microns in thickness. Just beneath the capsule is a layer six to eight cells deep of normal parathyroid chief cells.

The predominant cell is an enlarged transition wasserhelle cell (Fig. 19). It varies from 10 to 15 microns in diameter, smaller than the typical wasserhelle cell and has a fairly sharply outlined cell membrane. The shape is for the most part polyhedral, although the cells are so closely packed that almost any kind of shape can be found. The nuclei are eccentrically placed, are large, 6–10 microns in diameter, round, with a sharp basophilic outline and filled with a large amount of chromatin. Most of the nuclei contain one large, deeply stained, eccentric nucleolus located close to the limiting membranes. In several there are as many as three definite nucleoli. The cytoplasm is almost completely vacuolated except for some pinkish, finely granular threads on the inner surface of the cell membrane. Fat granules are present in all the parenchymal cells.

Irregularly scattered through the section are focal groups of cells similar to, but distinguishable from, the predominant type. One of these foci, an area 1.5 mm. in diameter, consists of cells with a cytoplasm which is much clearer, cell outlines sharper, and nuclei slightly smaller and more basophilic. The cells in this area might easily be regarded as true water-clear cells. The other focal areas are similar to each other and consist of cells resembling the predominant cell, except that the cytoplasm is stained uniformly light pink. There are several of these groups throughout each section, averaging 0.1–0.15 mm. in size.

A few dark oxyphil cells are scattered singly through the rim of normal tissue and among the vacuolated cells nearby. No oxyphil cells are apparent in the central portion of the tumor. There are a few, very small, colloid-filled vacuoles among the cells just beneath the capsule, but none among the vacuolated cells.

The cells are arranged in pseudoglandular formation, groups of approximately five to twenty-five being closely packed and surrounded by fine connective tissue strands, some of which contain small capillaries. None of these groups of cells shows demonstrable lumina, so that they cannot be called true alveoli. Many of the smaller groups have a single celled layer arranged radially, suggesting rosette formation. The stroma is scant, although there is one

area in which a collection of large fat cells similar to those in the normal parathyroid is seen.

CASE 22 (34–2649). *Clinical History:* H. C. B., a female, 26 years of age, had an attack of left renal colic accompanied by hematuria in June, 1933, followed in the course of a year by three or four similar attacks. There were no other symptoms. She entered the Massachusetts General Hospital in June, 1934, where a left ureterolithotomy was performed. The serum calcium was 12 mg., serum phosphorus 2.65 mg. X-rays of the skeleton were negative. The urine showed a slight trace of albumin and many calcium phosphate casts. A renal function test showed 35 per cent excretion. On July 6, 1934, at operation the right lower parathyroid gland was found enlarged and was removed. A frozen section showed a tumor of the chief cell type. One normal gland was seen in the left upper region. Because of the frozen section diagnosis and the finding of one normal gland, a more extensive exploration was not done. When the patient was discharged the calcium was 10.06 mg., the phosphorus 3.64 mg.

Gross Description: An encapsulated, smooth surfaced, orange-brown soft mass weighing 0.16 gm. and measuring 1 by 0.7 by 0.4 cm.

Microscopic Examination: Around more than one-half of the tumor is a small rim of normal parathyroid tissue. The capsule of the tumor is composed of thick acellular connective tissue measuring approximately 0.5 mm. in thickness. The cells are all of the same type, transitional wasserhelle cells, similar to those seen in Case 3. They average 15–20 microns in diameter with nuclei 10–15 microns in diameter. Many of the cells are much larger and contain as many as seven nuclei. There are occasional small intracellular fat granules. Glycogen is present in all the cells but much more marked in the cells in the rim of normal tissue.

CASE 8 (32–4330). *Clinical History:* A. R., a female, 44 years of age, developed pain in the right hip in 1931. X-rays at the Huntington Hospital in March, 1932, showed an extensive destructive process in the right ilium. There was no appreciable decalcification of the skeleton. The serum calcium was 14 mg., the serum phosphorus 1.5 mg. A diagnosis of hyperparathyroidism was made by Dr. J. C. Aub and treatment with high calcium diet produced improvement of symptoms. X-rays taken at the Massachusetts General Hospital in November, 1932, showed a localized area of rarefaction and areas of increased density were seen in the right ilium and a stone in the right kidney pelvis. On Nov. 30, 1932, a tumor lying against the trachea on the right side posterior to the thyroid was excised. She had very slight postoperative tetany.

Gross Description: A slightly flattened, ovoid, brownish red, slightly lobulated, soft, encapsulated piece of tissue measuring 2 by 0.8 by 0.6 cm. The cut surface is glistening and brownish red.

Microscopic Examination: The capsule is thin, measuring approximately 30–35 microns, and is composed of acellular fibrous connective tissue. Except for a few places, the immediate subcapsular area is made up of enlarged chief cells, measuring 11–15 microns in diameter. These are usually several layers deep but in some places only a thin rim one to three cells deep.

The arrangement of these cells is variable; some are arranged in small compact masses, some in double or triple rows with a slight tendency to palisading, and others in definite alveolar formation. The connective tissue stroma is very vascular and the capillaries and vessels are congested with polymorphonuclears and red cells.

Toward the central portion of the tumor the cells become more vacuolated, almost reaching the stage of true wasserhelle cells. These transition wasserhelle cells comprise about one-fourth of the total volume.

The most striking feature of this case is the predominance of the oxyphil cells. They are scattered throughout the whole tumor but are more conspicuous near the periphery, occurring for the most part in large groups, although single and small groups of cells are seen everywhere. One group is consistent with the pale oxyphil cell. The other type of eosinophilic cell is more often single, larger, measuring 17–20 microns, polyhedral in shape, has a moderately clear outline and is more deeply stained. The nucleus is small, round, sharply demarcated, hyperchromatic, eccentrically placed and measures about 6–7 microns in diameter. The cytoplasm is deep pinkish red and filled with tiny darker red granules. These cells are similar to those found in the normal parathyroid gland — typical dark oxyphil cells — except that they are much larger. No mitoses are seen.

The stroma, which contains occasional mast cells, is composed of moderately cellular, highly vascular connective tissue, but very little fat. There are occasional collections of lymphocytes and also small, unidentified, pink-staining, granular ovoid masses which do not simulate colloid.

CASE 12 (33–3876). *Clinical History:* Y. D., a female, 51 years of age. In 1925 a left nephrectomy for calculi was performed. She continued to pass gravel intermittently for a number of years. In 1930 a stone was removed from the pelvis of the right kidney. X-ray 1 year later showed a duodenal ulcer. In June, 1933, X-ray showed a stone in the right kidney. The serum calcium was 11.78 mg., phosphorus 4.35 mg., phosphatase normal. A right nephrotomy was performed but she continued to have colicky abdominal pains. A stone was present

in the lower ureter when she was seen 2 months later. There were no bone symptoms. On Oct. 7, 1933, a small parathyroid tumor located just below the sternal notch was removed. A large thyroid adenoma palpated preoperatively was also removed. She developed moderate tetany when the serum calcium dropped on the second postoperative day to 9.03 mg. When last seen, in 1934, the serum calcium was 9.88 mg., phosphorus 3.01 mg. and she felt well.

Gross Description: A small, encapsulated, ovoid mass measuring 1 by 0.4 by 0.2 cm. The surface is pinkish gray and coarsely granular. The cut surface is homogeneously purplish red.

Microscopic Examination: The capsule is very thin and in places not evident. Scattered throughout are large areas of fresh hemorrhage apparently due to operative trauma. At one corner of the section there is a small semilunar-shaped rim of normal parathyroid chief cells. The remainder of the section is made up of the tumor.

The cells comprising the tumor are of two types, the transition chief cell and the wasserhelle cell. The former makes up most of the specimen and shows all gradations from the chief to the wasserhelle cell. The cytoplasm of most of the cells, however, is not so clear as that of the cells of the previous 2 cases (Cases 3 and 22). The true wasserhelle cells, many of which contain no demonstrable nucleus, are compactly grouped in circumscribed islands and are much larger than the transition wasserhelle cells. The tumor resembles certain portions of Case 8, in which foci of wasserhelle cells are prominent, but is more similar to Case 3.

CASE 14 (33–4618). *Clinical History:* M. R., a male, 52 years of age, had an attack of renal colic with slight hematuria in 1923. Similar attacks recurred in 1927 and 1929, and in April, 1933, he developed left costovertebral pain with chills and fever. One month later a left ureterolithotomy was done. The serum calcium was 15.09 mg., phosphorus 2.84 mg. X-rays in November, 1933, showed diffuse skeletal decalcification without cyst formation and small indefinite areas of calcification in the lower poles of both kidneys which were not present in May, 1933. On Nov. 29, 1933, a parathyroid tumor was removed from behind the right lobe of the thyroid just above the inferior thyroid artery. When last seen, on Dec. 4, 1933, the serum calcium was 10.51 mg., phosphorus 2.54 mg.

Gross Description: An elongated, encapsulated, kidney-bean-shaped tumor weighing 1.2 gm. and measuring 2.2 by 1.8 by 0.9 cm. The tumor is divided in about its midportion by a jagged horizontal line. The upper half is yellow, smooth surfaced, but definitely divided into cystic lobules 3–4 mm. in diameter. By transillumination small yellowish white specks are seen floating in a clear fluid. Aspiration shows that the cyst is multilocular and about 0.5 cc. of a

slightly viscid yellow fluid is withdrawn. The lower half of the tumor is solid reddish brown and smooth surfaced. The cut surface is brownish yellow and moist.

Microscopic Examination: Just beneath the rather thin capsule in one area is a small semilunar rim of normal parathyroid tissue. The remainder of the specimen is composed of transition wasserhelle and true wasserhelle cells. The appearance is similar to Case 12, except that in this case the wasserhelle cells are more numerous than the transition cells.

The large cyst and a few smaller cystic spaces are all lined by wasserhelle cells. Most of them are filled with granular débris; an occasional small one contains colloid.

Summary of Cases 3, 22, 8, 12 and 14 (Transition Wasserhelle, Chief Cell Type)

The cells in these 5 cases are predominantly of the transition wasserhelle cell type — a stage between the chief and wasserhelle cell (Fig. 19). Cases 3, 8 and 22 are closer to the true wasserhelle cell, while Cases 12 and 14 are closer to the chief cell. Small fat granules are present in Cases 3, 8 and 22, but not in 12 and 14. The cells are all closely packed together and have no glandular arrangement. In 4 of the cases there is a rim of normal parathyroid tissue surrounding the tumor. Oxyphil cells are absent in all cases except Case 8. The latter has in addition slightly enlarged chief cells arranged in pseudoglandular formation.

CASE 10 (33–1943). *Clinical History:* M. S., a female, 54 years of age, developed at the age of 15 years severe "backstrain," which in light of subsequent events may have been a spontaneous fracture of a vertebra. Since then she had experienced frequency and incontinence of urine, culminating in 1932 in severe abdominal pain associated with increased disturbance of urination. There was loss of weight and appetite. Cystoscopy revealed a vesical calculus which was removed by cystotomy. Her renal function was poor. During convalescence routine blood studies showed that the serum calcium was 13.93 mg., serum phosphorus 2.98 mg., and phosphatase 3.4 units. The bones showed some decalcification by X-ray but no cystic areas. Relief from abdominal pain followed the operation, but increasing pain in the thighs made worse by walking led to a second hospital entry for further study of the hyperparathyroidism. On May 24, 1933, at operation a tumor lying adjacent to the left lower pole of the thyroid gland was removed. It was roughly twenty times larger than the normal inferior parathyroid which was seen on the right side. There was no tetany and convalescence was uneventful. On June 1, 1933, the serum calcium was 10.47 mg., serum phosphorus 3.85 mg. When last seen, on July 22, 1933, the patient had gained 12 pounds since operation and stated that she had not felt so well for years.

Gross Description: A pear-shaped, flattened, slightly firm, orange, encapsulated and pedunculated tumor 3 by 1.7 by 0.8 cm. The pedicle measures 1 by 1 by 0.4 cm. On one surface is a raised nodular area 3 mm. in diameter. The cut surface is uniformly yellowish brown and moist.

Microscopic Examination: The capsule is moderately thickened, measuring approximately 0.5 mm. It is composed of connective tissue strands between which are large numbers of congested vessels and many large fat cells.

This tumor is composed predominantly of two types of cells, similar to each other and both obviously related to the chief cell. There is, however, a definite dividing line between them.

The first type comprises a comparatively small proportion of the tumor and simulates the wasserhelle cell. The cell is polyhedral in shape with a fairly sharp pink outline and measures 10–14 microns in diameter. The nucleus is round, usually eccentric, sharply outlined, deeply basophilic, contains a moderate amount of chromatin and measures 7–9 microns in diameter. Except for a scanty, light pink, reticular cytoplasm, usually peripheral, most of the cell body is vacuolated. A few are completely vacuolated, but in general they have not reached the stage of true wasserhelle cells. No mitotic figures or multinucleated cells are seen. A small number of fat droplets are found in some of the cells. The stroma in this portion of the tumor is vascular. The capillaries are markedly congested with red cells and are so numerous that they often give the appearance of diffuse hemorrhage in between small groups or columns of cells. There are also larger endothelial-lined spaces, many of which are filled with a blue-staining, granular débris. No colloid or oxyphil cells are seen in this area.

The other and predominant part of the tumor is composed of slightly larger cells measuring up to 22 microns in diameter and averaging 15 (Fig. 20). Although these cells are not so sharply outlined as the others, many, neverthleless, have a sharp pink cell border. The nuclei, often multiple, are rounder, sharply outlined, for the most part centrally located, deeply basophilic and hyperchromatic and measure 8–10 microns in diameter. The most striking difference between the two cell types is in the cytoplasm, which shows almost no vacuolization and completely fills the cell body. There are no mitoses. The arrangement of the cells is also different. Here a large

proportion of the cells is arranged in well defined glands, averaging 65 microns in external diameter, with a lumen measuring about 22 microns in diameter. The single layer of lining cells is definitely cuboidal in character rather than polyhedral.

Many of the glands contain dark reddish pink, opaque, colloid-like masses, some completely filling the lumen, others only partially so. Some of the larger lumina show marginal vacuolization. Between these glands the stroma is scanty, but small endothelial-lined vessels, many filled with red cells and granular débris, are found. Occasional colloid droplets are seen in the connective tissue stroma. A small number of fat granules is seen in the cells, stroma and lumina. Although no true oxyphil cells are found, the predominant cell slightly suggests a transition stage to the oxyphil type.

CASE 19 (34–1526). *Clinical History:* T. G. Y., a male physician, 49 years of age, noted in January, 1932, the onset of malaise and muscle pains. In the course of 2 years he grew weaker and lost about 15 pounds in weight. Three months later he broke his clavicle during slight exertion. Slight nocturia had been noted for 5 years, but no gravel. Renal function test showed 30 per cent excretion. The serum calcium was 15.01 mg., phosphorus 2.61 mg., and phosphatase 14.1 units. X-ray showed changes in the bones characteristic of hyperparathyroidism and a questionable displacement of the esophagus to the left just above the sternal notch. On April 24, 1934, at operation a tumor arising close to the right inferior thyroid artery and extending backward and medially was subtotally resected, leaving a piece about twice the size of a normal parathyroid. The tumor had displaced the esophagus, as visualized in the X-ray film. The following day the serum calcium was 11.16 mg., phosphorus 1.25 mg., and phosphatase 13.2 units. When last seen, on June 15, 1934, he felt much better. The serum calcium was 8.04 mg., the phosphorus 3.82 mg.

Gross Description: A reddish brown, smooth surfaced, slightly lobulated and flattened, ovoid mass weighing 11.7 gm. and measuring 4 by 3 by 1.5 cm. Two small calcified areas 2–3 mm. in diameter project from the surface. One margin of the specimen is notched. The cut surface is homogeneously reddish brown and moist.

Microscopic Examination: A small rim of normal parathyroid tissue partially surrounds the tumor but is not separated from it by any definite fibrous tissue capsule.

The whole tumor is composed of a single type of cell which is polyhedral in shape, faintly outlined, and measures 11–16 microns in diameter. The cytoplasm is non-vacuolated, pinkish red, coarsely granular and completely fills all of the cell around the nucleus. The nucleus is round to ovoid, has a sharply demarcated basophilic out-

line, measures 6–8 microns in diameter and is usually eccentrically placed. The chromatin content is not very great and there are no mitoses. The cells contain no fat or glycogen. The appearance slightly resembles both the chief and pale oxyphil cell types, suggesting a transition stage.

The cells are closely packed in a manner similar to the arrangement of normal pale oxyphil cells but not, however, in islands or in palisade formation. The stroma contains no fat and is composed for the most part of large numbers of congested vessels, producing a pseudoglandular effect.

Summary of Cases 10 and 19 (Transition Oxyphil, Chief Cell Type)

These two tumors are composed predominantly of transition pale oxyphil cells, a stage between the chief and pale oxyphil cells (Fig. 20). They are arranged in glandular and pseudoglandular formation. No true oxyphil cells are present. One part of Case 10 has in addition a large area of transition wasserhelle cells.

CASE 4[6, 5] (32–3542). *Clinical History:* N. B., a female, 41 years of age, developed in 1925, following her fifth pregnancy, weakness in the back and knees and pain in the legs on walking. These symptoms increased with her sixth pregnancy in 1927, during which treatment for fallen arches was instituted. The diagnosis of "bone disease" made by her physician when she fractured the right femur in 1928 became obvious the following year when fractures of the right clavicle and later the right humerus occurred. In 1930 she entered the Massachusetts General Hospital where X-rays showed marked decalcification of the skeleton, cyst formation, old pathological fractures and a renal calculus. The serum calcium was 14.25 mg., phosphorus 2.3 mg. On Sept. 12, 1930, operation was done. The search, which was limited to the immediate region of the thyroid gland, failed to reveal a tumor but two normal parathyroid bodies were removed. A high calcium diet with viosterol gave improvement in symptoms and X-ray showed an increased deposit of calcium in the skull. As evidence of hyperparathyroidism persisted she returned to the hospital. At a second operation on Sept. 28, 1932, a large tumor was found behind the esophagus on the surface of the deep cervical fascia and a subtotal resection performed. She had moderately severe tetany during convalescence. In December, 1932, the serum calcium was 8 mg., phosphorus 4 mg., and phosphatase 4.3 units. When last seen, on Aug. 8, 1933, her anemia had improved and she felt much better.

Gross Description: An elongated, encapsulated, nodular mass of firm brown tissue measuring 3 by 1.5 by 0.9 cm. The cut surface is homogeneously reddish brown.

Microscopic Examination: The predominant cell in this case is the slightly enlarged chief cell (see Cases 6, 7 and 9). These cells are dis-

tributed in several ways. The major portion of them form the lining of large numbers of glands and cystic spaces (Fig. 21), which show great variations in size, some as small as 45 microns and others as large as 1 mm. Several of these spaces are partially or completely filled with a light pink, finely granular material, but many contain homogeneous, pink-staining material which slightly suggests colloid, an impression reinforced by the presence of marginal vacuolization, such as is seen in the hyperplastic thyroid. However, the light color and the lack of real density is more in favor of coagulation of the finely granular material rather than colloid. This same material, somewhat more deeply stained, is also found throughout the stroma, in many places completely obliterating the interstitial tissues. Some of these spaces are wholly or partially filled with red cells and occasional chief parathyroid cells, which may be desquamated lining cells. The lining is usually a single cell layer, but there is a fair number with two and even three layered linings. A few contain fat droplets.

Between these glandular structures are large collections of the same cells. Connective tissue stroma often containing small capillaries separates these collections of cells into small groups, many of which are pseudoglandular, and are composed on the average of about twenty-five to fifty cells, with occasional small lumina. Small groups of these cells, 5–10, arranged in gland formation resemble fetal adenomas of the thyroid. In several places the acinar cells show some degree of papillary infolding. In other areas the cells are arranged in undulating columns of three to four rows, the intervening stroma being composed of a fine reticulum. A tendency to palisading is barely recognizable. No mitoses are seen.

Scattered throughout all sections are pale oxyphil cells arranged in large groups varying in size from 0.1 mm. to 7–8 mm. The cells are slightly larger and less uniform than the normal oxyphil cell, varying from 8 to 17 microns. The cell outlines are fairly distinct, reddish pink and round to polyhedral in shape, clearer than the chief cell, but much less sharp than the wasserhelle cell. The nucleus is ovoid, deeply basophilic, sharply demarcated, centrally placed, hyperchromatic and fills about one-quarter of the cell volume. An occasional cell is multinucleated. Because of the large quantity of chromatin it is often difficult to distinguish a definite nucleolus. The cytoplasm is pink and granular, and usually fills the cell, although occasionally there is a small halo around the nucleus. Occasional, single dark oxy-

phil cells, usually located near the stroma, are found interspersed among the pale oxyphil groups.

The stroma of the glandular portion is composed of relatively dense fibrous tissue and large collections of colloid-like material. In the compact and pseudoglandular areas it is much less fibrous, but vascular.

CASE 13 (33–4182). *Clinical History:* A male, 22 years of age, was perfectly well until October, 1932, when he developed painless hematuria. In March, 1933, an attack of right renal colic was followed by the passage of a stone 2 weeks later, but several more attacks, one of them on the left side, pointed to the presence of additional stones. Physical examination was negative. The serum calcium was 15.78 mg., phosphorus 2.8 mg., phosphatase 4 units. Following X-ray of the urinary tract a right nephrolithotomy was performed. On Oct. 28, 1933, at operation a small parathyroid tumor under the upper pole of the left lobe of the thyroid was removed. On the fifth postoperative day the serum calcium was 10 mg., phosphorus 2.32 mg. When last seen, on Dec. 1, 1933, he was well, did not tire at the end of the day as he had done before, and felt much stronger.

Gross Description: A moderately soft, smooth surfaced, well encapsulated, slightly flattened, round tumor mass measuring approximately 1.7 cm. in diameter and weighing 2.1 gm. The surface is slightly mottled pale to orange-brown. The cut surface is moist, yellow to pinkish brown. The periphery is light brown to yellow.

Microscopic Examination: The capsule is quite thick, measuring up to 2 mm. in places, and is composed of fibrous connective tissue in which are numerous, endothelial-lined empty spaces. In addition there are many more unlined spaces that are partially or completely filled with parathyroid chief or wasserhelle cells. A tempting though uncertain interpretation is to regard these spaces as capsular lymphatics containing tumor cells. In any event there is definite evidence of parathyroid cells within the capsule. In one place there is a large group of wasserhelle cells just beneath the capsule. One end of this group of wasserhelle cells definitely invades the capsule and divides it for some distance into two layers. In the outermost layers of the capsule, and in one area very close to the outer surface of the capsule, there are chief cells arranged in glandular formation. Although this picture strongly suggests capsular invasion, it can also be interpreted as a rim of normal parathyroid tissue which has been markedly compressed by the tumor.

Just beneath the capsule are small and large foci of closely packed wasserhelle cells. The nuclei lie in the corner of the cell that is closest

to the stroma, giving the whole area a pattern similar to that seen in Case 16, where the whole gland has the same appearance. Many of the cells have no nuclei.

Except for the above mentioned capsule and subcapsular areas the specimen is composed of chief cells arranged in marked cystic and glandular formation, similar in parts to the glandular section of Case 4 (Figs. 22 and 23). There are no oxyphil cells. The cells are arranged in fairly compact masses and surround large numbers of cystic, irregular, papillary spaces, varying from 0.1 to 3 mm. in diameter. In many places these cystic spaces are lined by only a single layer of chief cells, but usually they are surrounded by the compact layers of the parenchymal chief cells. Some of these spaces are empty; many contain pink-staining granular débris; others are filled with red cells. The stroma is fairly abundant, contains many small vessels and no fat cells.

CASE 18 (34–1387). *Clinical History:* J. F., a female, 58 years of age. In 1924, 10 years before admission, the patient fractured her left femur after severe trauma, and had remained lame. In 1933 she fainted while at stool, fell, and broke the left femur again and also the left humerus. There were no genito-urinary symptoms. X-rays showed bone decalcification. The serum calcium was 11.36 mg., phosphorus 2.53 mg., and phosphatase 5.75 units. On April 13, 1934, at operation a tumor lying on the terminal divisions of the right inferior thyroid artery was resected. When last seen, on April 23, 1934, the calcium was 9.31 mg., phosphorus 3.32.

Gross Description: A flattened, almond-shaped, smooth surfaced mass 1.2 by 0.8 cm. by 0.4 cm. At one pole there is a semilunar area approximately 3 by 2 by 1 mm. which is yellowish brown and which is taken to be normal parathyroid tissue. The remainder of the specimen is dark purplish red and soft. This was thought to be tumor, although a hematoma in a normal gland could not be ruled out.

Microscopic Examination: A rim of normal parathyroid tissue surrounds the tumor. The dark purplish area observed grossly is a very vascular tumor. All the vascular channels, both small and large, are dilated and congested, producing a pseudo-acinar and in places papillary effect. The latter is further emphasized by the presence of numerous, irregularly shaped cystic spaces into which villus-like groups of cells project. Many of these spaces are empty, others filled with granular débris or red cells, and a few with colloid.

The cells are all of the chief and transition wasserhelle variety. No true wasserhelle cells are seen. Pale and dark oxyphil cells are absent. There are occasional intracellular fat droplets, but no intercellular fat globules such as are seen in the rim of normal parathyroid.

Summary of Cases 4, 13 and 18 (Glandular Cystic, Chief Cell Type)

These 3 cases are composed predominantly of slightly enlarged chief cells lining and surrounding numerous cystic and glandular spaces (Figs. 21, 22 and 23). This process is more prominent in Cases 4 and 13. Case 4 has in addition many islands of pale oxyphil cells. A rim of normal parathyroid tissue is present in Cases 13 and 18.

CASE 2 (32–157). *Clinical History:* M. L., a female, 60 years of age, experienced in 1928 a pain in the back which was intensified by motion, and followed by swelling and pain in the shoulder, knee and ankles. In February, 1931, a diagnosis of mild hypertrophic arthritis and osteomalacia was made. Serum calcium was 10.4 mg., phosphorus 3.6 mg. Treatment with a high calcium diet and viosterol resulted in considerable relief of symptoms, though the pain in the ankles and the aching in the knee continued and she was still subject to fatigue and inability to work. The diagnosis was temporarily changed to osteoporosis because of the consistently low phosphorus. Careful studies showed slight but constant elevation of serum calcium and low phosphorus, and a diagnosis of hyperparathyroidism was made. At operation, on Jan. 14, 1932, the right lower parathyroid body appeared considerably larger than normal and was removed. Convalescence was uneventful, without tetany. Serum calcium was 10.65 mg., phosphorus 3.68 mg. When last seen, on May 27, 1933, she was optimistic, felt much better and was working.

Gross Description: A smooth surfaced, moderately firm, ovoid, brownish mass measuring 10 by 5 by 4 mm.

Microscopic Examination: A section is taken through the whole mass. Under low power one sees a well circumscribed, encapsulated tumor, on one side of which is a peripheral zone of normal parathyroid tissue (Fig. 15). The tumor makes up about five-sixths of the specimen.

The capsule of the tumor is composed of a thin layer of acellular fibrous tissue. At one end of the section is a large, recent hemorrhagic area between the capsule of the tumor and the surrounding normal parathyroid tissue. In one place the hemorrhage has apparently broken through the capsule and is seen in the tumor.

The predominant cell is the typical wasserhelle cell (Fig. 16), measuring between 17 and 22 microns. The shape is usually poly-

hedral, but in the closely packed areas may be variable. The cell outline is a thin, sharp pink line, much more conspicuous than that of the normal parathyroid chief cells. The nucleus is eccentrically placed in one corner of the cell, is also sharply outlined and is deeply basophilic. It is round in shape, either clear or opaque, and measures about 8 microns. The nucleolus is just to one side of the center, is fairly conspicuous, and is surrounded by a large number of chromatin granules. Occasionally no nucleus is seen.

The cells are completely vacuolated, entirely lacking in demonstrable cytoplasm but contain moderate numbers of fat droplets. They can be regarded only as wasserhelle cells. In general the cells show no definite arrangement, although a single gland is noted. No mitotic figures are found.

In each section there are two to three large collections of cells which simulate the wasserhelle cells. They are about the same size and have a similar nucleus. The cell outline, however, is poorly defined and the cytoplasm is composed of a fine, reticular-like, pink cytoplasm in which are scattered, coarse, more brightly pink-stained granules. They have not the homogeneous cytoplasm of a true pale oxyphil cell, but may be a transition form (see Cases 10 and 19).

No oxyphil cells are found in the tumor, although they are present in fair numbers in the surrounding normal parathyroid tissue.

The stroma is scant and made up almost solely of fine capillaries and occasional small, vacuolated spaces, 11–15 microns in diameter, which contain homogeneous, pink-staining, colloid-like masses. One portion of the tumor contains a number of large fat cells similar to those seen in the surrounding normal parathyroid tissue.

Summary of Case 2 (Neoplasia: Wasserhelle, Generalized)

An encapsulated tumor composed predominantly of wasserhelle cells, scattered among which are a few large collections of probable transitional oxyphil cells. There are no mitoses or multinucleated cells. There is a rim of normal parathyroid around a portion of the tumor (Figs. 15 and 16).

CASE 5 (32–3594). *Clinical History:* R. T., a female, 55 years of age. In 1922 the patient developed attacks of severe pain in the right flank, radiating to the epigastrium, for which the gall-bladder was removed in 1927. The attacks not only were not relieved but became more severe. She was easily fatigued. In September, 1932, at the Massachusetts General Hospital a stone, shown by

X-ray in the pelvis of the right kidney, was removed by pyelotomy. Routine blood chemistry studies showed the serum calcium to be 13.2 mg., phosphorus 2.78 mg., phosphatase 5 units. On Oct. 3, 1932, a parathyroid tumor below the left lower pole of the thyroid was resected. A mild tetany was present postoperatively. When last seen, on Dec. 9, 1932, the serum calcium was 10.34 mg., phosphorus 3.71.

Gross Description: A slightly firm, reddish, and in places orange, slightly ecchymotic, encapsulated tumor measuring 1.5 by 1 by 1 cm. The cut surface is homogeneous, smooth, glistening and orange to reddish gray.

Microscopic Examination: The capsule is thin. Under low power one can see fairly large circumscribed masses of wasserhelle cells scattered at intervals through the tumor, which is elsewhere composed of chief cells (Fig. 24). These masses vary in size from 0.1 to 1.5 mm. in diameter. The subcapsular portion contains large collections of dark oxyphil cells.

The wasserhelle cells probably make up more than half the tumor. They are polyhedral, closely packed and measure 11–20 microns in diameter (Fig. 24). Their cell outlines are thicker than normal, reddish pink and ragged, but are easily seen because of the vacuolated cytoplasm. The nucleus is large, measuring 8–11 microns, eccentrically placed, round, sharply circumscribed, deeply basophilic, and so packed with chromatin that in many instances the nucleolus cannot be made out. The cytoplasm for the most part is completely vacuolated. A few cells contain pink-staining, coarsely granular débris, others lighter but brighter pink, homogeneous clear droplets 3–5 microns in diameter. No fat droplets are seen. There are no mitoses. Scattered among these cells are a few that have a light pink granular cytoplasm. These may well be transitions between the chief cell and the fully developed wasserhelle cell. No true oxyphil cells are found in the wasserhelle groups. The stroma between these wasserhelle cells is scant, but where it is present definite endothelial-lined vessels containing red blood cells are found. A few of the colloid-like droplets are also found in the stroma. Scattered throughout are irregularly shaped small spaces, which vary from 15 to 90 microns, most of them empty, but some containing pink-staining débris and others red blood cells.

Around the wasserhelle groups are slightly enlarged chief cells arranged for the most part in compact masses, in a few areas toward

the periphery in well formed glands with walls one to three cells deep, many of which are filled with red cells. Near the periphery, where the chief cells predominate, the stroma is markedly congested and contains large globules of fat.

Groups of typical, normal dark oxyphil cells are found close to the periphery, while single ones are distributed throughout the gland, except among the wasserhelle cells.

Summary of Case 5 (Neoplasia: Wasserhelle, Focal)

An encapsulated tumor composed of both chief and wasserhelle cells (Fig. 24). The latter are arranged in circumscribed masses making up more than half the tumor; the former are smaller and arranged in compact masses and in a few places in glands. There is very little fat in either type of cell.

CASE 20 (34–2321). *Clinical History:* N. M. K., a female, 36 years of age, in 1928 had her first attack of renal colic followed by a similar attack 3 months later. In 1930 stones were removed from the left kidney and right ureter but she continued to have attacks of renal colic. In 1933 she was delivered of a healthy full term child, following which she passed many small stones and developed polydipsia. There was no history of bone or joint pains or loss of weight. She entered the Massachusetts General Hospital in May, 1934. The urine was loaded with white and red blood cells, and had a fixed low specific gravity. The phenolsulphonephthalein test showed 40 per cent excretion. The serum calcium was 12.16 mg., phosphorus 3.27 mg. and the phosphatase 6–8 units. On June 13, 1934, at operation both upper parathyroid glands were found enlarged and were removed; both lowers were normal in size and a biopsy of each was taken. Serum calcium and phosphorus taken 7 hours postoperatively were 9.56 mg. and 2 mg. respectively. Mild tetany developed on the second postoperative day. When discharged, on June 25, 1934, the serum calcium was 10.62 mg., the serum phosphorus 4.52 mg.

Gross Description: (Right Upper): A yellowish brown, with reddish mottling, encapsulated mass 1.3 by 0.7 by 0.3 cm., weighing 0.28 gm.

(Left Upper): A light brown, flattened, round encapsulated mass measuring 1 by 0.8 by 0.3 cm. and weighing 0.3 gm. The biopsies from the lower glands are light brown in color and measure about 1 mm. in diameter.

Microscopic Examination: (Right Upper): The thin capsule is composed of acellular fibrous connective tissue and no rim of normal parathyroid tissue can be demonstrated around the tumor. The blood vessels are markedly congested and in addition there are many

large extravascular collections of red blood cells. The predominant cell throughout the tumor is a typical enlarged chief cell with the usual ill-defined cell outline and large hyperchromatic round nucleus, similar to that seen in Case 6. The cells average 10 microns in diameter, the nuclei 7 microns. The arrangement is protean. There are compact masses, anastomosing cords running between dilated capillaries of sinusoidal appearance, and large areas of gland formation. Many of the glands are lined with chief cells resembling the bulk of the tumor. Other glands, however, are of a totally different appearance, resembling none that we have seen in any of our other cases.* The lining cells here do not resemble chief cells. They are columnar in shape with basal nuclei and a rather localized area of vacuolization which does not surround the nucleus but always lies in the opposite pole of the cell toward the lumen of the gland. The appearance closely simulates the duct of a mucous gland lined by goblet cells. Both types of glands are filled with red cells (Fig. 26). Wasserhelle cells are completely, and pale and dark oxyphil cells practically, absent. In an occasional area normal pale oxyphil cells surround some of the glands.

The stroma is for the most part scant, with wide and thin-walled capillaries and many foci of hemorrhage, but in a few places several isolated cells are surrounded by irregular areas of almost acellular, richly collagenous fibrous tissue. There are no intercellular fat droplets. A small amount of colloid is present.

(*Left Upper*): This gland is quite different from the right upper (Figs. 25 and 26). In this instance a rim of normal parathyroid tissue containing many large fat cells in its stroma surrounds the tumor and is separated from it by a fairly thick connective tissue capsule. The cells are all of the same type — the transitional wasserhelle cell. There are a few intracellular fat droplets. Glycogen is present in normal amounts. Except for the absence of true wasserhelle cells, this specimen is similar to Case 12. There are no pale oxyphil cells and only an occasional normal dark oxyphil cell. All the cells are massed compactly together with little stroma. In a few places near the periphery there is a slight tendency to pseudo-alveolar arrangement and a slight resemblance to the pattern observed in the hyperplastic group.

* Case 24 in the Massachusetts General Hospital series, which is not reported in this paper because operation was performed after the paper was submitted, shows a single adenoma with this same histological picture.

The biopsies from the two lower glands show normal parathyroid tissue.

CASE 21 (34–2362). *Clinical History:* E. T., a female, 35 years of age, had an attack of left renal colic followed by the passage of a stone in November, 1933. Three months later several stones were removed at a local hospital. X-rays of the skeleton were normal. Following operation she felt well except for easy fatiguability and occasional low backache. She entered the Massachusetts General Hospital in June, 1934. Physical examination was negative. A renal function test showed 65 per cent excretion in 2 hours. The serum calcium was 11.92 mg., serum phosphorus 2.86 mg. On June 16, 1934, at operation the right lower parathyroid was found enlarged and was resected. The right upper was about the same size and a small biopsy of it was taken. No parathyroid tissue was found on the left side, even after the left lobe of the thyroid had been removed and carefully examined. On June 17th the serum calcium was 8.6 mg., phosphorus 3 mg. On the second postoperative day she developed mild tetany which lasted only a few days. When discharged, on June 26, 1934, the serum calcium was 10.34 mg., phosphorus 2.9 mg. A stone was still present in one kidney.

Gross Description: (*Right Lower*): A moderately firm, yellowish brown encapsulated mass 1 by 0.6 by 0.3 cm. The cut surface is uniformly yellowish brown. (*Right Upper*): A small biopsy approximately 2 mm. in diameter.

Microscopic Examination: (*Right Lower*): Around one edge of the tumor is a small rim of normal parathyroid tissue composed of chief cells and several large fat globules. The capsule of the tumor is thin. The tumor is composed for the most part of two types of cells, chief and pale oxyphil, with a slight predominance of the oxyphils. The chief cells of the tumor measure about 10–12 microns in diameter, the nuclei 8–10 microns; those in the rim of normal tissue measure 7–8 microns with nuclei of 5–6 microns. The cytoplasm is only slightly vacuolated and contains an occasional tiny fat granule and a normal amount of glycogen. There are no extracellular fat globules. The arrangement of the tumor cells is pseudoglandular. In many places, however, pale oxyphil cells are adjacent to chief cells, but almost all the latter are true chief cells and not in transitional stages to pale oxyphils. Glycogen is present in normal amounts. In addition to the scattered, single, pale oxyphil cells many of them are arranged in large islands. This finding is unusual in a person 35 years of age.

The biopsy of the upper gland shows a similar picture.

Summary of Cases 20 and 21 (Neoplasia: Multiple)

In each of the 2 cases two tumors were found composed predominantly of chief cells. In Case 20 one is definitely glandular; the

other is non-glandular, made up wholly of the transition wasserhelle cell and has a rim of normal parathyroid tissue. In Case 21 both tumors have the same appearance and contain many pale oxyphil cells, both single and in large groups.

Review of the Literature

One hundred and sixty cases of probable hyperparathyroidism have been collected from the literature and the significant data tabulated (Table VI, see page 50). We have attempted to include all tumors and tumor-like enlargements of the parathyroid glands but have excluded from the series cases of osteomalacia, rickets, and primary nephritis in which slight secondary parathyroid hyperplasia is frequent. Rigid proof of hyperparathyroidism is often lacking, but in cases of marked parathyroid enlargement the burden of proof rests on the disclaimer.

Many of the case reports are regrettably incomplete, either in the clinical or in the anatomical details, and this considerably limits the value of the table. Knowledge of the syndrome of hyperparathyroidism has developed slowly and although the association of a parathyroid tumor with bone lesions was reported as early as 1903 by Askanazy,[10] it was not until 1913 that the combination began to be noted by a significant proportion of writers on the subject. Even at the present time the association with renal stones is still largely unrecognized and the experience in our clinic strongly indicates that more attention devoted to this phase of the disease will greatly increase the proportion of cases in which renal calculi are reported.

Statistical Data

Age

Including our series the ages are stated in 176 cases.

Table I

Distribution per Decade

Age in years	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89
Total cases	0	11	28	29	44	43	12	8	1
Adenomas	0	10	25	27	37	38	11	5	1
Hyperplasias ...	0	1	3	2	7	5	1	3	0

The highest incidence of hyperparathyroidism is between 40 and 60 years of age. There is no significant difference in this regard between the group of localized tumors and the group of diffuse hyperplasias. Although the youngest case recorded is 13 years of age (our Case 3), the symptoms in this patient were clearly of at least 4 years duration, so that the occurrence of the disease in the first decade is to be expected in rare instances.

Sex

Sex is reported in 174 cases.

TABLE II

Sex Incidence

	Females	Males
Total	122	52
Adenomas	108	45
Hyperplasias	14	7

The predominance of females over males is evident in both groups, being in a ratio of approximately two and a half to one for the adenomas and exactly two to one for the hyperplasias.

Number of Glands Enlarged

TABLE III

Data on Enlarged Glands

Available cases	185
Single gland enlarged	146
Multiple enlargements	39
(*a*) Two glands	25
(*b*) Three glands	1
(*c*) Four glands	13

Site

The data are distinctly inadequate. Of 119 single tumors in which location is recorded, 56 were on the right and 47 on the left. In 76 cases an attempt was made at more accurate localization and of these, 12 adenomas were found in one of the upper glands and 64 in one of the lower glands. This five to one ratio is of evident surgical value. Tumors of aberrant parathyroid glands are by no means infrequent — 6 have been found within the thyroid, 2 in the thymus,

and 9 have been described as retrosternal. Where two glands have been reported as enlarged any combination is possible, but again the lowers have been more frequently involved than the uppers.

Size

The sizes of the tumors vary over an extreme range. Symptoms of hyperparathyroidism have been recorded with a tumor only twice the size of a normal gland. At the other end of the scale tumors have been recorded weighing as much as 300 gm. and Benjamins [18] described one as large as a "child's head."

Incidence of Osteitis Fibrosa and Renal Stones

The presence of bone lesions is recorded in 116 of the 160 cases collected in Table VI, but in only 4 of the remainder were they specifically stated to be absent. A glance at the table where the cases have been listed in the order of their publication will show how rarely the relation was recognized by the earlier writers. Since an analogous situation still prevails in regard to renal stone formation, we have listed our cases separately in the following table. The value of routine blood calcium and phosphorus determinations in all cases of renal stone formation (Albright *et al.*[5]) is at once evident when the percentage of calculi in this series is compared with that in the previously reported cases. We have included only the cases in which a definite statement in regard to bone lesions was recorded.

TABLE IV

Incidence of Osteitis Fibrosa and Renal Stones

	Present series		Cases in literature	
	No.	% of total (25)	No.	% of total (119)
Osteitis fibrosa alone	5	20	70	58.8
Renal stones alone	11	44	3	2.52
Osteitis fibrosa plus stone	9	36	46	38.6

When our own series of cases is divided into the hyperplastic and the adenomatous groups, 13 of the latter showed bone lesions, whereas the 5 clear cell hyperplasias fall into the group of renal stones without bone changes and only Case 23A, the chief cell hyperplasia, showed significant bone lesions. That this is the result of chance

sampling in too small a series of cases is at once apparent by reference to the group of 14 clear cell hyperplasias collected from the literature, all but 1 of which showed bone lesions. It is evident that either type of hyperparathyroidism may be associated with stone formation only, bone changes only, or the combination. As a rule stone formation comes first and bone lesions follow only after a period of years. When the average duration of symptoms in our cases showing only renal stones is calculated, it is 3.2 years, whereas the average duration in the cases with classical bone lesions is 8.6 years.

Classification

As we have already briefly outlined in the introduction to our own series of case reports, we believe the fundamental line of division in the pathology of hyperparathyroidism lies between diffuse hyperplasia of all the parathyroid tissue and localized proliferation of only a portion, the remaining glandular tissue being histologically normal. In the first type diffuse enlargement of all the glands is to be expected; in the second type one or at most two will be involved. The division, however, judging from our own experience and the reports of others, cannot safely be made upon the number of grossly enlarged glands in each case. The degree of enlargement of individual glands varies greatly and though slight enlargement of every gland is probably always present in hyperplasia, the swelling of one or two glands may be so predominant that minor enlargement of the others might readily be overlooked, particularly under the exigencies of a surgical operation. In cases, however, where portions of all the parathyroids have been examined microscopically, as in Cases 17, 23, 25 and 23A of our series, and 32, 36 and 53 from the literature, the uniformity in histological appearance of all the glands, whether large or small, is at once apparent.

Fortunately, however, the histological picture of the hyperplastic gland, at least of the more common wasserhelle type, is so characteristic, so different from anything we have seen in the cases of single tumor formation that we believe a diagnosis of hyperplasia should be possible as a rule from the histological examination of a single gland, even from a frozen section during an operation. The uniform, giant sized clear cells, the acinar arrangement, the basal orientation of the nuclei form a readily recognizable picture (Figs. 8–11).

That hyperplasia of a different type, uniform proliferation of chief cells without significant vacuolization, can occur is shown by our Case 23A (Figs. 12 and 13) and by Cases 29 and 61 from the literature. Hyperplasia of this type, marked enough to cause significant tumor-like enlargement of the glands, is evidently rare since including our own case we have been able to find only three examples.

Another potential source of error in classification, if gross enlargement only is considered, lies in the confusion of multiple neoplasms with hyperplasias. Numbers 20 and 21 of our series are, we believe, cases in point. In Case 20 all four parathyroids were exposed at operation, two which were enlarged were resected and from the other two, which appeared normal, biopsies were taken. The biopsies show normal parathyroid tissue. The two enlarged glands are shown in Figs. 25 and 26. In contrast to the hyperplastic cases where every gland presents a uniform appearance, one of these tumors is frankly glandular in character, the other consists of solid masses of chief cells without evident arrangement. In Case 21 two tumors of identical appearance, the familiar chief cell adenoma, were found, but a rim of normal gland about one of the tumors definitely rules out diffuse hyperplasia. Bergstrand[21] twice demonstrated a rim of normal gland about each of a pair of localized tumors.

An attempt to classify the cases from the literature is admittedly dangerous but by limiting ourselves to cases in which a reasonably complete histological description is recorded or in which adequate illustrations allow us to judge for ourselves, we believe that a fairly accurate classification is possible. That several of the cases may have been misplaced is frankly admitted. One hundred and twenty-eight cases from the literature have been utilized. To these have been added, besides our own series of 25, an additional 9 unreported cases from other hospitals which the authors have been given the privilege of examining histologically.* In compiling the table single glandular enlargement has been automatically placed in the neoplastic group, cases with three or four enlarged glands in the hyperplastic one. Where two glands were enlarged we have attempted classification on the basis of the histological features. Five cases of multiple enlargement, 37, 62, 94, 141 and 159, we have felt unable to classify.

* These 9 cases, all single tumors, are distributed as follows: chief cell alone 3, chief cell with giant forms 1, transition wasserhelle 2, glandular and cystic 1, wasserhelle generalized 1.

The localized enlargements or neoplasms have been subdivided first into single and multiple groups and then classified on purely morphological grounds. The sequence of the classification (Table V)

TABLE V

Classification of Cases

	Case Nos. in our series	No. in our series	No. in literature	Percent of total
A. Hyperplasia (multiple) (22 cases)				13.6
1. Wasserhelle, generalized	15, 16, 17, 23, 25	5	14*	
2. Chief	23A	1	2†	
B. Neoplasia (140 cases)				86.4
1. Single (128 cases)				
(*a*) Chief cell types (114 cases)				
(1) Chief cell alone	6, 7, 9	3	59	
(2) Chief cell with giant forms	1, 11	2	3	
(3) Transition wasserhelle	3, 22, 8, 12, 14	5	17	
(4) Transition oxyphil	10, 19	2	6	
(5) Glandular and cystic	4, 13, 18	3	14	
(*b*) Wasserhelle cell types (14 cases)				
(1) Generalized	2	1	11	
(2) Focal	5	1	1	
2. Multiple (12 cases)				
(*a*) Chief cell types	20, 21	2	7	
(*b*) ? Oxyphil cell			3	
		25	137	

* Case Nos. 22, 23, 25, 32, 36, 53, 89, 92, 98, 123, 125, 126, 127, 155.
† Case Nos. 29, 61.

follows the order in which the case reports have been presented above.

Out of a total of 161 cases 22 or 13.6 per cent appear to belong in

the hyperplastic group, 19 of which are in the wasserhelle type as against 3 in the chief cell type. The far commoner localized tumor formation is represented by 140 cases, 86.4 per cent of the total, 130 of them single tumors, 10 of them multiple. In the single tumors the chief cell with its transition forms accounts for at least 90 per cent.

Discussion

Hyperplasia versus Neoplasia

Since the recognition of the syndrome of hyperparathyroidism, the question whether to regard the proliferative changes in the glands as hyperplastic or neoplastic has been a matter of controversy which the paucity of available evidence served only to stimulate. The demonstration of a distinct group of cases characterized by diffuse uniform involvement of all parathyroid tissue is, we believe, the first unequivocal evidence bearing on this issue. Such diffuse involvement points so strongly to hyperplasia dependent on a generalized humoral stimulus (possibly though improbably with mediation of the nervous system), and so strongly against a local autonomy that neoplasia cannot be seriously considered. The recognition, moreover, of at least two distinct histological types of hyperplasia not only suggests the interesting possibility of multiple potential stimulating factors but confirms the essential pattern of the hyperplastic lesion — the uniform diffuse involvement of all the glandular tissue. The analogy to exophthalmic goiter is of course apparent.

In sharp contrast to this relatively uncommon type of case stands the far more usual type of a localized proliferative process which leaves entirely uninvolved the remaining glandular tissue. Let us first consider several suggestive but inconclusive histological criteria favoring the neoplastic origin of the localized tumors (which our cases illustrate). All of them have been repeatedly cited before, but they rise in importance by their comparison with known hyperplastic lesions.

Cell size and number of nuclei fail to provide distinguishing criteria since rather surprisingly the hyperplastic group provides the largest cells and the most frequently multinucleated. But among the group of localized tumors an occasional example is encountered of gigantism of the nuclei up to 20 microns (Fig. 18) associated with an irregular multilobulated outline and extreme hyperchromatism,

which has no parallel in the hyperplastic state and which has a certain *prima facie* neoplastic quality.

In comparison with the rather monotonous uniformity as a group and also from field to field of the hyperplastic cases the localized tumors present a protean picture not merely as a group, but also at times within the dimensions of a low power field of a single tumor. Tumors may be made up almost solely of chief cells (Fig. 17), of fully developed wasserhelle cells (Fig. 16), of transitional wasserhelle (Fig. 19), of transitional oxyphil cells (Fig. 20), or any combination of these elements. Well developed gland formation will be present in one area, broad anastomosing cords in another and solid patternless cell masses in a third.

Fibrous stroma which is scant but uniform in its distribution in the normal gland increases in the hyperplastic gland to strands of uniform width which surround each acinus and sharply demarcate it from its neighbors. In the localized tumors, in contrast, it is markedly irregular in character and distribution, here abundant and richly collagenous, there tenuous and barely demonstrable. Blood vessels which are constant in size in the normal gland, rather uniformly increased in number and diameter in the hyperplastic gland, become irregular in caliber and distribution in the tumor nodules. A sinusoidal dilatation of capillary vessels is a frequent abnormality. Endothelial-lined spaces, probably lymphatics, which are undemonstrable in normal and hyperplastic glands, are frequently conspicuously dilated.

The crux of the argument rests, in our opinion, in the localized character of the proliferative process. Our own experience indicates this is frequently limited not merely to one gland but to a portion of a single gland. In 8 of our 19 adenomatous cases we have been able to demonstrate a rim of normal parathyroid tissue on one margin of the tumor. That this has been noted in the literature on only eight occasions can be explained we feel on two bases: (1) it has not been systematically looked for, and (2) our cases for the most part are early ones with relatively smaller tumors than the majority that have been reported. It is obvious that the mathematical chances of demonstrating a small fragment of normal parathyroid tissue in or on the capsule of a tumor diminish rapidly with increase in size of the tumor. Partial or total atrophy of the normal remnants is, moreover, not improbable with tumors of large size.

If an external humoral stimulus to overgrowth is present in these cases, it must be of minimal importance compared with the local autonomous factor which determines the site of the proliferative activity. Moreover, if the newgrowth were in response to a persisting outside stimulus, surgical removal should logically be followed by reasonably prompt recurrence of the growth process in one of the other remaining glands. Surgical experience does not support this in a wide experience with the localized tumors. In the realm of typical hyperplasias experience is still limited, but the short follow-up on our Cases 15 and 23 strongly suggests an extrinsic factor. In Case 23, three enlarged glands and a biopsy of a normal sized fourth gland were removed, following which the serum calcium fell from 13.1 to 10.18 mg. Three months later the serum calcium was 11.96 mg. Case 15, in which three enlarged glands were removed, with a drop of serum calcium to 11.4 mg., is awaiting further treatment with a serum calcium that has risen once more to 13.8 mg.*

We can, therefore, distinguish on the available evidence between two groups of proliferative changes in the parathyroid glands, one primarily dependent on an external, continuous stimulus, the second independent, as far as can be made out, of such a stimulus, determined in its localization and duration by local autonomous factors which can be extirpated by local surgical removal. This second type of proliferation, an essentially autonomous newgrowth, falls within the accepted limits of the term neoplasia.

Comparison of the Size of Hyperplastic Glands and Adenomas with the Degree of Hyperparathyroidism

The degree of hypertrophy of glandular tissue in cases of parathyroid hyperplasia is in itself worthy of attention. The material removed from Case 16 of our series, the severest of our hyperplastic cases, amounted to 15.6 gm. This is approximately one hundred times the weight of the total normal parathyroid tissue. A degree of hyperplasia equal to this is totally unparalleled in human pathology. In exophthalmic goiter, in mazoplasia or in prostatic hyperplasia five or tenfold hypertrophy would be unusual. Even lactation hypertrophy of the breast is left far behind.

* A fourth gland in this case was not found and all of the third gland, except for a piece twice the size of a normal gland, was resected.

In the case of parathyroid adenomas still greater variations occur. In our Case 1 the tumor weighed 53 gm., approximately four hundred times the normal, and much larger tumors are on record. If this newformed glandular tissue functioned in proportion to its size, some individuals would die of parathyroid poisoning, like that so easily produced in animals with parathormone,[77] unless some compensating mechanism were brought into play. An answer to the problem must await biological assays of material from both hyperplastic and adenomatous glands.

That a roughly quantitative relation between size of tumor and degree of hyperfunction exists is apparent from the following figures. Since weights were lacking on several of the cases, we have compared the volumes.

(5 cases) Blood calcium less than 12 mg. Average volume 255 cmm.
(9 cases) Blood calcium 12 to 14 mg. Average volume 3830 cmm.
(8 cases) Blood calcium greater than 14 mg. Average volume 16,000 cmm.

It is evident that as the size of the tumor increases the proportional effect of unit weight on the blood calcium becomes rapidly less and less. In fact in the hyperplastic cases the relation appeared to approach a logarithmic function. The hyperplasias, as might be expected from their histological uniformity, show a more nearly mathematical relation. The adenomas in contrast show far wider variations. All attempts to correlate the degree of hyperfunction with the histology of the tumors have proved fruitless.

Function

Throughout the history of endocrinology the study of tumors of the ductless glands has played an important rôle, sometimes pointing the path to chemical researches, as in the case of the pituitary adenomas, sometimes bringing up the rear to give final confirmation to an already well understood mechanism, as in the pancreatic islet adenomas. The multiplicity of cell types in the parathyroid glands naturally makes one think of the pituitary. Does the study of parathyroid tumors aid us in understanding the histophysiology of the normal organ?

In the normal gland there is general agreement, and our own studies are in accord, that glycogen can invariably be found at any age and is present in every type of cell except the fully developed

oxyphil. Unfortunately, material was not suitably preserved for glycogen stains in all of our cases, but we have available at least 1 case of each type and as yet have not failed to demonstrate at least some granules. As a general rule it is less abundant in both the tumors and the hyperplasias than in the normal gland (in adenomas with normal tissue in the capsule this is often strikingly apparent) but in at least some cells of every tumor it will be found. It is apt to be most evident in the cells that approach most nearly the normal chief cell in appearance. It is present in the wasserhelle cells and it is least marked or absent in the cells that most nearly approach the normal oxyphils. We can, therefore, say that glycogen has been found present whenever sought for in every case of hyperfunction. This reinforces the fact that it is invariably present in the normal gland and suggests that glycogen is in some way necessary to the elaboration of the specific hormone.

Fat droplets within the parenchymal cells are in contrast entirely lacking in the normal glands of children and cannot, therefore, be necessary to the elaboration of the hormone by which the calcium balance is maintained. In confirmation, intracellular fat has been present in some of our adenomas, absent in others.

Fat cells in the stroma cannot seriously be considered to have any direct bearing on the function of the gland. They remind one naturally of the bone marrow, and their relative independence of the state of nourishment of the individual might suggest a similar function, a readily resorbable tissue permitting rapid and facile hyperplasia. In hyperplastic glands it entirely disappears; in the adenomas it is usually absent though occasional fat cells can be found.

Have the oxyphil cells a function? Certainly their presence is not necessary to the normal functioning of the gland since they appear only with middle age and do not become numerous until advanced life. Oxyphil cells are wholly absent from the hyperplastic physiologically overactive gland. True oxyphils may be wholly absent from the adenomas; they may be scattered in small numbers much as they are distributed in the normal gland of early adult life; they may be present in localized collections similar to the oxyphil islands of old age. Transition oxyphils, according to our classification cells with large amounts of homogeneous red cytoplasm but still with traces of vacuolization about the nucleus, may make up the bulk of a tumor, but among them cells which closely approach the chief cell type have

always been found. We have been unable to classify any of our cases as a true oxyphil adenoma and although cases have been so classified by other authors, we have not found their descriptions convincing. Turnbull's case of oxyphil adenoma (Case 93), for instance, clearly shows from an illustration some degree of halo formation about the nucleus. He himself speaks of the presence of glycogen and fat, though he has never been able to demonstrate these substances in the typical oxyphil cells of normal glands. We feel, therefore, that it can fairly be said that histological evidence fails to support the concept of the elaboration of parathyroid hormone by the oxyphil cells. The frequency of these cells in tumors, even in young people, their absence in hyperplasias, their increase under normal conditions in old age, all point toward an involution phenomenon. The possibility of another function, unconnected with the calcium metabolism cannot be ruled out, but we have found no evidence for it.

Interrelation Between Cells

Since Welsh's fundamental study of the histology of the parathyroid glands, the interrelation of the various cell types has been under discussion. He sharply separated the oxyphil cell but believed in transitions between the water-clear and the chief cell, though he considered the former the more primitive type, in contrast to later workers, such as Getzowa,[56] who have felt that if one were derived from the other, it was the chief cell which was the primitive form.

With Kurokawa [85] the possibility that the oxyphil also was derived from the chief cell was considered and various transition forms were described. Hunter and Turnbull [80] have developed this concept, stating that "the oxyphil cells are principal cells in which the cytoplasm has been so charged with oxyphil granules that the basophil net has been more or less completely reduced to a limiting membrane."

Does a study of the tumors of the parathyroid glands contribute any evidence for or against a monophyletic development of the various cell types? As Hunter and Turnbull have pointed out, the normal evolution of the gland in fetal and adolescent life, starting only with chief cells, with successive development of water-clear cells, of pale oxyphils and dark oxyphils with the simultaneous appearance of transition forms argues for a single fundamental cell type. The clear

TABLE VI

Summary of Case Reports from the Literature

Author	Year	Age in yrs.	Sex	No. of tumors	Site	Size in cm.	Weight in gm.	Bone change	Renal stone	Cell type	Comment
1. de Santi	1900	58	M	1		Very large				No histology	
2. Benjamins	1902	57	M	1	R	Child's head				Chief	
3. Askanazy	1903	51	F	1	L	4.5 × 2		+	+	Chief	
4. Erdheim	1903	18		1	RL	2.5 × 1.5 × 1.5				Chief	
5. MacCallum	1905	26	M	1	RL	2 × 2 × 2				Chief (occasional wasserhelle)	
6. Hulst	1905	old	F	1	In thyroid	2.5 × 2.5 × 2				Transition wasserhelle	
7. Weichselbaum ...	1906		M	1	RL	2.5 × 1.5 × 1.5					Died of pneumonia
8. Weichselbaum ...	1906		F	1	LU	4.3 × 3.6 × 1				? Glandular and cystic	Died of pneumonia
9. Langhans	1907	58	M	1		13 × 9 × 8				Wasserhelle generalized	Operation for goiter
10. Langhans	1907	60	F	1		10 × 8 × 2				Wasserhelle generalized	Operation for goiter
11. von Verebély	1907	42	F	1	RL	2.5 × 1.8 × 1.5				Chief (occasional wasserhelle)	
12. von Verebély	1907	56	M	1	LL	1.2 × 0.8 × 0.3				Wasserhelle generalized	
13. Schmorl	1907	48	F	1	LU	2.8 × 1.8 × 0.5		+		Chief	
14. Thompson and Harris	1908	23	F	1		15 × 10 × 6	250			Chief	Operation for goiter

15. Bérard and Alamartine ...	1908	43	F	1	L	2 × 1.5				Chief (occasional wasserhelle)	
16. Pepere	1907	40	F	1	LU	Apple sized				Chief	
17. DaCosta	1909	32	F	1	R	Orange sized				Glandular and cystic	Operation for goiter
18. Strada	1909	54	F	1	R	2.8 × 1.4 × 0.9		+	+	Chief (occasional wasserhelle)	4 other glands slightly enlarged. ? osteomalacia
19. Claude and Schmiergeld ...	1909	85	M	1	RL	1.5 × 0.7 × 0.5				Wasserhelle generalized	Epilepsy
20. da Costa	1909	50	F	1	RL					Glandular and cystic	
21. Gussio	1910	30	F	1	L	Small mandarin				Chief	
22. Möller	1911	72	F	2	LU RU	2 × 1.2 × 1 0.8 × 0.6 × 0.4				Wasserhelle generalized	Lowers not found
23. Möller	1911	46	F	2	LU RU	4.5 × 0.5 × 0.5 4.5 × 0.5 × 0.5				Wasserhelle generalized	Miliary tuberculosis
24. Ikonnikoff	1912	57	F	1	In thyroid	Mandarin				Chief	
25. Gjestland	1912	75	M	2	RL LL	4 × 1 Hazel nut		o	o	Wasserhelle generalized	Uppers slightly enlarged
26. Schmorl	1913	72	M	1	U			? Paget's		No histology	
27. Molineus	1913	74	F	1	R	2.7 × 1.7 × 0.7		+		Transition wasserhelle	

R = right; L = left or lower; U = upper.

TABLE VI (*continued*)

Author	Year	Age in yrs.	Sex	No. of tumors	Site	Size in cm.	Weight in gm.	Bone change	Renal stone	Cell type	Comment
28. Molineus	1913	59	F	2	LU RL	2.7 × 1.8 × 0.8 2.7 × 1.8 × 0.8		+		Chief (? transition wasserhelle)	2 others normal
29. Molineus	1913	48	F	4	RU RL LU LL	1.8 × 1.2 × 0.2 1.9 × 1.7 × 0.8 1.6 × 0.4 × 0.3 2.3 × 1.1 × 1.2		+		Chief (papillary)	
30. Paltauf	1913	51	F	1	RL			+		Chief	3 others normal
31. Harbitz	1915	26	F	1	L	3.5 × 3.5 × 2		∓	+	Chief	Called osteomalacia
32. Harbitz	1915	75	M	4	RU RL LU LL	4 × 1 Pea 2 × 2.5 1 × 1.2				Wasserhelle generalized	Paralysis agitans
33. Harbitz	1915	32	F	1	LL	11 × 5				? transition oxyphil	Died of tuberculosis
34. Maresch	1916	69	M	1	L	7 × 4 × 1.5		o		Glandular and cystic	3 others normal
35. Meyer	1917	36	M	1	RL	4 × 3		+		Chief	3 others normal
36. Bergstrand	1920	57	F	4			0.40 0.15 0.08 1.04	o	o	Wasserhelle generalized	Died of pneumonia
37. Hubbard and Wentworth ...	1921	20	F	2		2 in diameter		+	+	Called hyperplasia	? renal rickets
38. Hartwich	1922	60	F	1	L	7 × 2.5 × 1	4.9	+		Chief (occasional wasserhelle)	Others normal

39. Nägelsbach and Westnes	1922	27	M	1		Pigeon's egg		+	+	No histology	Others normal
40. Günther	1922			1	RL			+		Chief	History lost
41. Fischer	1922	46	M	1	RL	3.7 × 2.7 × 2		+		No histology	
42. Strauch	1922	27	F	1	L	4.8 × 3.2 × 3.5				? oxyphil (wasserhelle)	Puerperal osteomalacia
43. Sauer	1922	21	M	1	LL	Hazel nut		+	+	Chief	Calcified capsule
44. Bergstrand	1922	21	F	2	RL LL		0.31 0.32			? transition oxyphil	Uppers normal. Thymus enlarged
45. Bergstrand	1922	58	F	2	RL LL		0.12 0.37			? transition oxyphil	Uppers normal. Thymus enlarged
46. Pachner	1922	52	F	1	L	15 × 10				? transition wasserhelle	
47. Dawson and Struthers	1923	49	M	1	LL	2.5 in diameter		+		Chief	
48. Fasiani	1923	65	F	1		Fist				Chief (occasional wasserhelle)	
49. Stenholm	1924	24	M	1	RL	1.8 × 1.2 × 1		+	+	Chief	3 others normal
50. Stenholm	1924	52	F	1	RL	3.3 × 1.9 × 1.1		+		Glandular and cystic	3 others normal
51. Chauveau	1925	50	F	1		Hazel nut		+		Chief	
52. Gödel, Leb	1925	42	F	2	LL RL	10 × 2 8 × 1.8		+	+	Chief (? transition wasserhelle)	
53. Hoffheinz	1925	42		4	RL RU LL LU	5.5 × 3.4 × 1.4 2 × 0.5 × 0.3 4.5 × 2.1 × 1.2 1.4 × 1 × 0.3				Wasserhelle generalized	

TABLE VI (*continued*)

Author	Year	Age in yrs.	Sex	No. of tumors	Site	Size in cm.	Weight in gm.	Bone change	Renal stone	Cell type	Comment
54. Penecke	1926	38	F	1	LL		16	+	+	? transition oxyphil	Chronic nephritis
55. Penecke	1926	59	F	1	RL		5			Chief	Erysipelas
56. Mandl	1925 1926	38	M	1	LL	2.5 × 1.5 × 1.2		+		Transition wasserhelle	
57. Parreira and Castro Freire	1926	16	M	1	R	Chestnut		+		Wasserhelle generalized	
58. Hendriock	1926	71	F	1	Retro-sternal	8 × 5 × 4.5				Wasserhelle	
59. Wanke	1926	31	F	1	RL	Chestnut		+	+	Chief	
60. Gold	1928	54	F	1	RU	2.5 × 1.6		+		Chief (? transition wasserhelle)	
61. Bergstrand	1928	48	F	4			Total 13.7			Glandular and cystic	Cerebral hemorrhage
62. Beck	1928	41	F	2	RL LL	Coffee bean Hazel nut		+		No histology	
63. Eggers	1929		F	1	LL	Hazel nut		+		No histology.	
64. Boyd *et al.*	1929	21	M	1	LL	3.5 × 2.5		+		Transition wasserhelle	
65. Barr *et al.*	1929	56	F	1	L	3 in diameter		+	+	Chief	
66. Barr *et al.*	1929	38	M	1		5 in diameter		+		Chief	

67. Guy	1929	29	F	1		8 × 6 × 4				Glandular and cystic	Recurred
68. Hunter	1929	41	F	1	LL	3·7 × 3 × 3		+		No histology	
69. Wellbrock	1929	32	F	1	Retro-sternal	5 × 3·5 × 3		+		Glandular and cystic	
70. Lloyd	1929	22	F	2	LL RL	1.7 × 1 × 0.8 1.5 × 0.4 × 0.3				Chief (occasional wasserhelle)	Pituitary tumor
71. Drennan	1930	63	F	1	RL	4.5 in diameter		+		Chief (occasional wasserhelle)	
72. Zajewloschin	1930	57	M	1	RL	4·3 × 3 × 1.3	8			Chief	Others normal
73. Pemberton	1930	14	F	1	LL	1.5 × 1.3 × 1.3		+		Chief	
74. Compere	1930	59	F	1	LL	1 × 1.8		+		Glandular and cystic	
75. Snapper	1930	56	M	1	LL	2.5 × 1.4		+		Wasserhelle generalized	
76. Rosenbach and Disqué	1930	24	F	1	RL			+		No histology	
77. Hecker	1930					Walnut		+		No histology	
78. Ask-Upmark	1930	46	M	1	L	1.5 × 1.2 × 1.2		+	o	Chief	
79. Léri *et al.*	1930	31	M	1	RL			+	+	Wasserhelle generalized	
80. Wanke	1930	38	F	1	RL	Walnut		+	+	Glandular	
81. Wanke	1930	41	F	2	RU RL	Coffee bean Almond		+	+	Chief	
82. Schupp	1931	51	F	1	In thyroid	1.5 × 0.5 × 0.8		+		Chief	3 others normal

TABLE VI (*continued*)

Author	Year	Age in yrs.	Sex	No. of tumors	Site	Size in cm.	Weight in gm.	Bone change	Renal stone	Cell type	Comment
83. Schouten	1931	55	M	1				+		No histology	
84. Silvestrini	1931	25	M	1	L	Olive		+		No histology	
85. Silvestrini	1931	57	M	1	L	1.5 × 2.5		+		No histology	
86. Allan	1931	34	M	1			10	+		No histology	
87. Snapper	1931	35	F	1	L	Almond		+		No histology	
88. Quick and Hunsberger, Schnabel	1931	25	M	1	Retro-sternal	5.2 × 3.5 × 2.5		+	+	Chief	Removed in two operations
89. Paul	1931	56	M	2	RU LU	6 × 3 × 3 6 × 3 × 3		+	+	Wasserhelle generalized	Adrenals enlarged
90. Cosin	1931	17	M	1	RU	2.7 × 2.2 × 2		+	+	Transition wasserhelle	
91. Hunter and Turnbull	1931	49	F	2	LU RL	1.1 in diameter 2.8 × 1.8 × 2.5		+	+	Chief with giant forms	
92. Hunter and Turnbull	1931	37	F	2	RU LL	2.3 × 1.5 × 0.9 1.4 × 0.8 × 0.5		+	+	Wasserhelle generalized	
93. Hunter and Turnbull	1931	49	F	1	LL	6.8 × 2.8 × 1.4	13.5	+	+	? oxyphil ? wasserhelle	
94. Hunter and Turnbull	1931	51	F	2	RU RL	7.5 × 5 × 1.8 2 × 1.3 × 1.2	26.2	+	+	Called oxyphil	

95. Lièvre *et al.*	1931	41	F	1	RL	3.5 × 3 × 2		+		? transition oxyphil	
96. Cooley	1931	14	F	1				+		No histology	
97. Ask-Upmark	1931	43	F	1	L	4 × 2.2 × 1		+		Chief	
98. Bergstrand	1931	55	F	2	LU RL	4.5 × 2.5 × 3 4.5 × 2 × 0.5		+	+	Wasserhelle generalized	2 others slightly enlarged
99. Berner	1931	40	F	1	L	1.8 × 1.8	7	+		Wasserhelle focal	
100. Berner	1931	47	F	1	L	3 in diameter		+	+	Chief (occasional wasserhelle)	
101. Fraser	1931	42	F	1				+		No histology	
102. Fraser	1931	26	F	1				+	+	No histology	
103. Fraser	1931	23	F	1				+	+	No histology	
104. Weil	1931	44	F	1	RL	3.1 × 2.2 × 1.6	4.3	+	+	No histology	
105. von Redwitz	1931			1	RL	Cherry stone		+		No histology	
106. May and Lièvre	1931	45	M	1	LL	3 × 2 × 0.8	1.8	+	+	Chief	
107. Chievitz and Olsen	1932	25	F	1	RL	3.5 × 2 × 0.5		+		Chief	
108. Noble	1932	40	M	1	LU	2 × 1.8 × 1.5		+	+	Transition wasserhelle	
109. Hadfield and Rogers	1932	58	F	1	L	5 × 3.5 × 3	52	0		? wasserhelle generalized	Acromegaly
110. Hadfield and Rogers	1932	51	M	1		8 × 4 × 2.5			+	Chief	Acromegaly

TABLE VI (*continued*)

Author	Year	Age in yrs.	Sex	No. of tumors	Site	Size in cm.	Weight in gm.	Bone change	Renal stone	Cell type	Comment
111. Gaudier and Patoir	1932	60	M	1	RL			+		Glandular	
112. Beyerinck	1932	35	F	2	R and L				+	Called tubular adenoma	1 at operation 1 at autopsy
113. Frugoni and Alessandri	1932	18	F	1	R	2.2 × 1.1 × 0.6	0.9	+		Transition wasserhelle	
114. Rosedale	1932	50	F	1	R	2 × 2.5	7	+		Transition wasserhelle	
115. Mertz	1932	70	F	1	RL	1 × 1 × 0.5		+		Glandular and cystic	
116. Mertz	1932	64	F	1	RL	Normal		+		Chief	Calcium high Phosphorus low
117. Mertz	1932	73	F	1	RL	1 × 0.5 × 0.5		+		Chief	
118. Morelle	1932	56	F	1	LL	6 × 6.8 × 4.2	67	+	+	Chief	
119. Coryn	1932	20	F	1	In thyroid	1.3 in diameter		+		Chief	3 operations to find tumor
120. Babcock	1932	25	F	1	LL	1.5 in diameter		+	+	No histology	
121. Wichmann	1932	45	F	1	LU	1.3 in diameter		+		Wasserhelle generalized	
122. Hellström	1932	42	F	1	LL	2 × 1.8 × 1.4		+		Chief	
123. Hellström	1932	44	F	2	R L	Walnut Walnut		+		Wasserhelle generalized	Removed at 3 months interval

124. Hanke	1932	33	F	2	R L	3.1 × 3 × 1.2 Hazel nut		+	+	Called oxyphil	
125. Hanke	1932	49	F	2	RL LL	5 × 3 × 2 Walnut		+	+	Wasserhelle generalized	2 others slightly enlarged
126. Gordon-Taylor ..	1932	20	F	2	R L	3.5 × 2.5 × 2.5 Enlarged		+		Wasserhelle generalized	
127. Wilder *et al.*	1932	48	F	1	RU	2 × 1.5 × 1		+		Wasserhelle generalized	3 others slightly enlarged. Same histology
128. Rusakov and Sakayan	1932	50	F	2	L R	Cherry stone 3 × 2 × 1		+	+	Chief (occasional wasserhelle)	
129. Renaud *et al.*	1932			1	Retrosternal	4 × 2.5		+		Chief (occasional wasserhelle)	
130. Cohen and Kelly	1933	48	F	1	RL	2.5 × 1.5 × 1	2.5	+	+	Chief	
131. Elmslie *et al.*	1933	42	F	1	LL	3 × 1.5 × 1.5		+	o	Transition wasserhelle	
132. Elmslie *et al.*	1933	26	F	1	R	2.5 × 2 × 2		+	+	Transition wasserhelle	
133. Elmslie *et al.*	1933	23	F	1	L	3.5 × 1.5 × 0.7		+	+	Chief	
134. Thomason and Smith	1933	41	F	1	LU	2.2 in diameter		+		Chief	
135. Struthers	1933	38	F	1	R	1.8 in diameter		+		? Chief	
136. Struthers	1933	48	F	1		1.8 in diameter		+	+	No histology	

TABLE VI (*continued*)

Author	Year	Age in yrs.	Sex	No. of tumors	Site	Size in cm.	Weight in gm.	Bone change	Renal stone	Cell type	Comment
137. Copello and Barlaro	1933	46	M	1	LL			+	+	Called adenoma	
138. Venables	1933	52	F	1	In thyroid	1.8 × 1.8 × 1.2		+		Called oxyphil	
139. Rankin and Priestly	1933	34	F	1	R	6 in diameter		+		Chief with giant forms	
140. Schlesinger and Gold	1933	42	F	1	In thyroid	5 × 4 × 4		+		Glandular and cystic	
141. Sainton *et al.*	1933	43	M	2	LL LU	Enlarged	2.1	+		? oxyphil ? wasserhelle generalized	Calcium high after a 1st operation. LU found at 2nd operation
142. Keynes and Taylor	1933	18	M	1	LL	3.5 × 2.5		+	+	Chief	
143. Dyke *et al.*	1933	14	F	1	LL	3 × 2 × 1		+		Transition wasserhelle	
144. Dyke *et al.*	1933	14	F	1	RL		5	+		Transition wasserhelle	
145. Abel *et al.*	1933	58	F	1	LL	4 × 1.8 × 1.6	4.3	+		Chief with ? giant forms	
146. Mandl	1933	47	F	1	Retrosternal	4 × 2.5 × 2		+		Chief	
147. Hand	1933	39	M	1	LL	4 × 2.5 × 2		o	o	Glandular and cystic	Pyelonephritis

148. Morton	1933	20	F	1	RL	2.1 × 1.8 × 0.5	1.3	+		Transition wasserhelle	Other glands negative
149. Schwensen and Eiken	1933	36	F	1		5 × 3.5 × 2	37	+	+	Chief	
150. Khurgina	1933	34	M	1	LL	2.5 × 1		+	+	Chief	Diffuse calcium deposits
151. Mimpriss and Butler	1934	17	M	1	Retrosternal	1.2 in diameter		+		Chief (occasional wasserhelle)	
152. Barker	1934	65	F	1	RL	2.5 × 2 × 1		+	+	No histology	
153. Strandgaard	1934	47	F	1	R	1 × 1.7	2	+	+	Transition wasserhelle	
154. Sørensen	1934	74	M	1	LL	1.5 × 3.5 × 2.5	7	+		Chief	
155. Capps	1934	50	M	2	RL LL	7 × 3.5 × 2.1 2.4 × 3.5 × 2.1	22 13.6			Wasserhelle generalized	
156. Gutman *et al.*....	1934	34	M	1	RL	2.7 × 1.6 × 1	3.5	+	? +	Chief	
157. Gutman *et al.*....	1934	53	F	1	RL	3 × 2 × 0.8	4.5	+	+	Wasserhelle generalized	
158. Gutman *et al.*....	1934	35	F	1				+		No histology	
159. Gutman *et al.*....	1934	60	F	2	RU RL	2 in diameter 1.5 × 0.7 × 0.4		+		Called oxyphil	
160. Bergstrand	1934	64	F	1	In thymus	Pigeon egg		+	+	Chief	4 others normal, adrenals enlarged, metastasizing thyroid adenoma

cell hyperplasias prove that a physiological stimulus can convert every parathyroid cell into the wasserhelle type.

The neoplasias of the glands serve to reinforce the arguments against genetically different cell types and favor the concept of a fundamental cell from which all others are derived. Pure tumors of either the oxyphil or wasserhelle type unaccompanied by any chief cell forms were not present in our series and we find the occasional reports in the literature unconvincing. When cells of either of these specialized types are predominant numerous transition forms of the chief cell can always be demonstrated. The chief cell in other words is the only invariable component of a tumor, obviously the basic fundamental cell and possibly the only proliferative form. The other cell types derived from it are to be regarded as degrees of differentiation or as involution forms.

Summary

The histology of the parathyroid glands in 25 cases of hyperparathyroidism has been reported in detail and contrasted with the normal glands removed from 150 routine autopsies. It was found possible to divide the cases sharply into two groups, one of them characterized by diffuse uniform changes throughout all the glandular tissue—an obvious hyperplastic process—the second by a proliferative area limited to one gland, frequently even to a portion of it, or rarely involving parts of two glands. For reasons which have been discussed at length in the text, we regard this localized type of growth as neoplastic.

On this basis a classification of the parathyroid changes in hyperparathyroidism into two primary groups, hyperplasia and neoplasia, with subgroups under each heading, based on the morphological criteria of predominant cell type and structure, has been proposed. It has been shown that this is applicable not only to our own series but to the entire group of 160 cases which we have been able to collect from the literature.

An effort has been made to compile adequate statistical data on the relative frequency of these types of hyperparathyroidism and also on age and sex incidence, the frequency of multiple growths, the location of the tumors and the relation of both types of the disease to osteitis fibrosa cystica and to renal stone formation. A rough quan-

titative relation between the size of the enlarged glands and the degree of hyperfunction has been demonstrated.

Finally, an attempt has been made to bring to bear such data as a study of parathyroid tumors affords upon the problems of the function and the histogenesis of the various cell types.

Conclusions

1. The pathological findings in the parathyroid glands in hyperparathyroidism may be divided sharply into two types, hyperplasia and neoplasia.

2. Hyperplasia is characterized by diffuse uniform involvement of all the glandular tissue. It occurs, however, in two forms, a wasserhelle or water-clear cell type, and a much rarer chief cell type.

3. Localized tumors of a single gland, part of a gland, or rarely parts of two glands, are more logically to be regarded as neoplasms.

4. A roughly quantitative relation between the size of the enlarged glands and the degree of hyperfunction exists.

5. The histology of parathyroid tumors provides confirmatory evidence for the monophyletic theory of origin of the various cell types.

6. Glycogen, albeit in minute amounts, is always present in functioning parathyroid tissue and the concept of the oxyphil cell as an inactive involution product receives support from a study of the adenomas.

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DESCRIPTION OF PLATES

PLATE 1

FIG. 1. A longitudinal section of a whole parathyroid gland from a child 16 months old, showing the compact grouping of the chief cells and the absence of fat. × 20.

FIG. 2. A longitudinal section of a whole normal parathyroid gland from an adult 40 years of age, showing the relative proportions of parenchymal and fat cells. × 15.

FIG. 3. A longitudinal section of a whole normal parathyroid gland from an adult 80 years of age, showing numerous circumscribed islands of pale oxyphil cells. × 15.

FIG. 4. A longitudinal section of a whole parathyroid gland showing a large cyst and two minute encapsulated adenomas. × 12.

FIG. 5. A longitudinal section of a whole parathyroid gland showing an apparently non-functioning, well circumscribed adenoma. Fat cells which are in normal numbers in the surrounding gland are nearly absent in the tumor. × 12.

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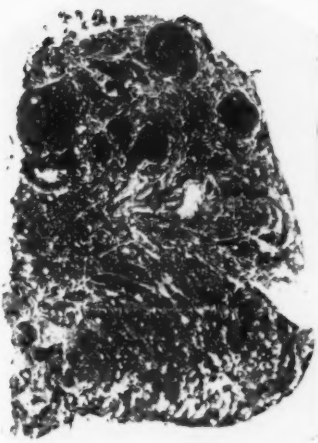

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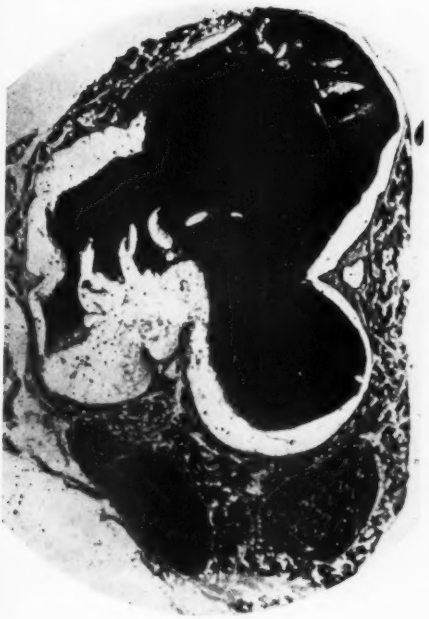

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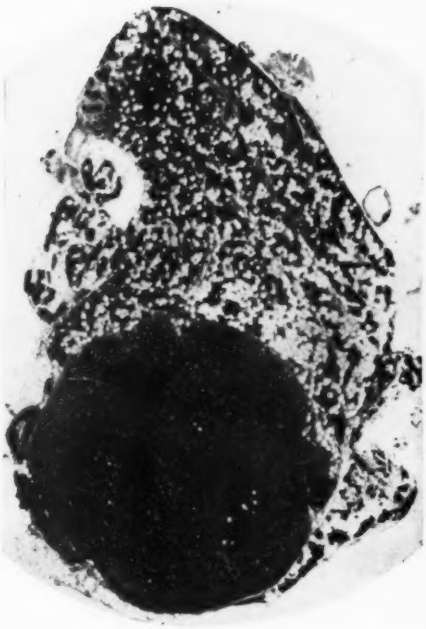

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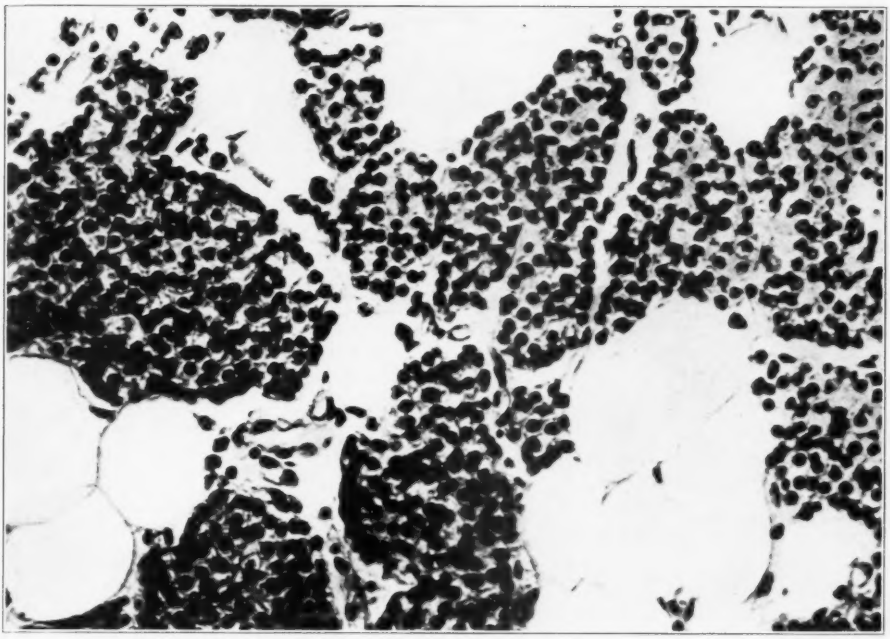
PLATE 2

FIG. 6. A higher magnification of a small portion of the gland shown in Fig. 2, showing the normal chief and large fat cells. × 400.

FIG. 7. A higher magnification of an island of pale oxyphil cells from the gland shown in Fig. 3. Note the surrounding normal chief cells and the lack of extracellular fat globules. × 400.



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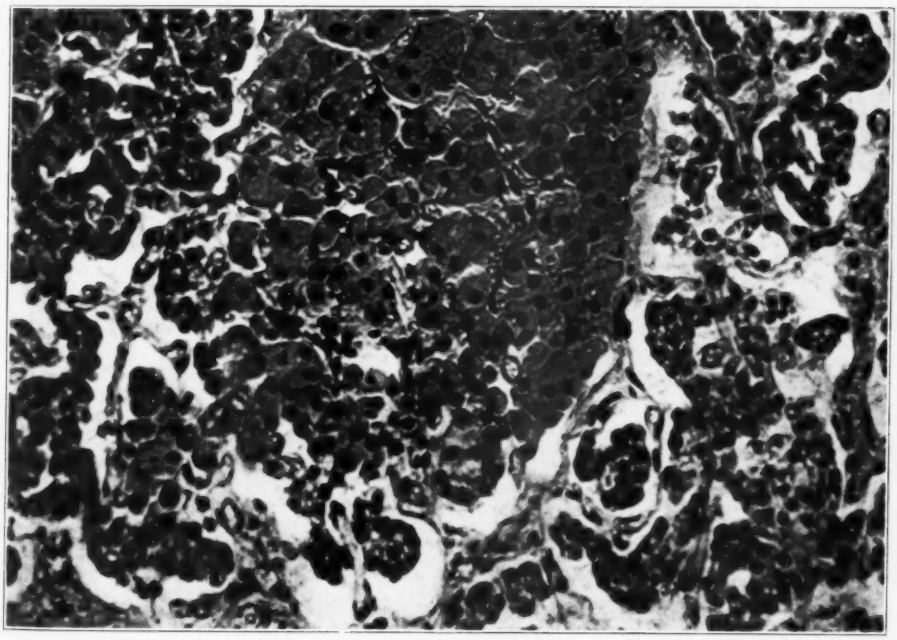

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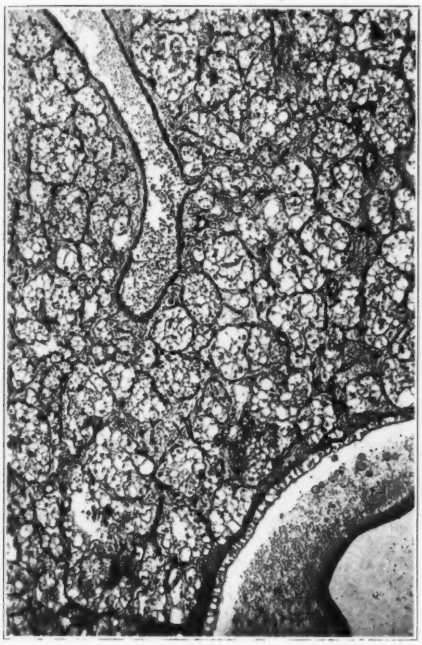
PLATE 3

FIG. 8. Case 15. A low power view of clear cell hyperplasia. The marked uniform acinar arrangement, the swollen clear cells, the abundant vascular stroma and the absent fat are characteristic. One huge cyst is present. × 50.

FIG. 9. A higher power of Fig. 8. Note the definite gland formation, the sharply outlined large epithelial cells, the cytoplasm absent except for scattered granules, and the dark basally oriented nuclei. × 400.

FIG. 10. Case 16. The typical pattern in a case of parathyroid hyperplasia produced by the basal orientation of the nuclei. × 50.

FIG. 11. A higher power of Fig. 10. The nuclei of many of the cells lie out of the plane of section. When present, they are hyperchromatic and clearly oriented toward the stroma. × 400.



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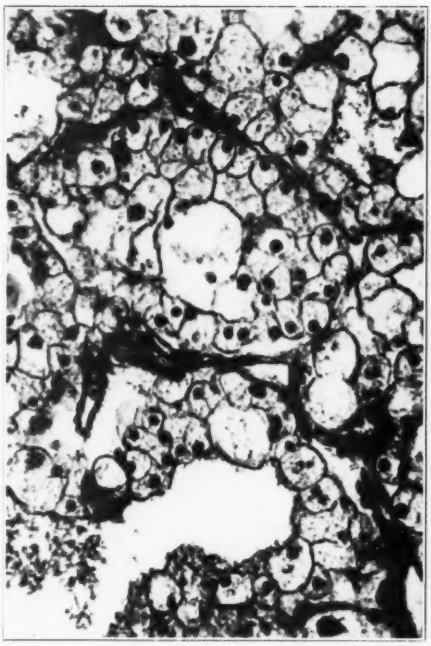

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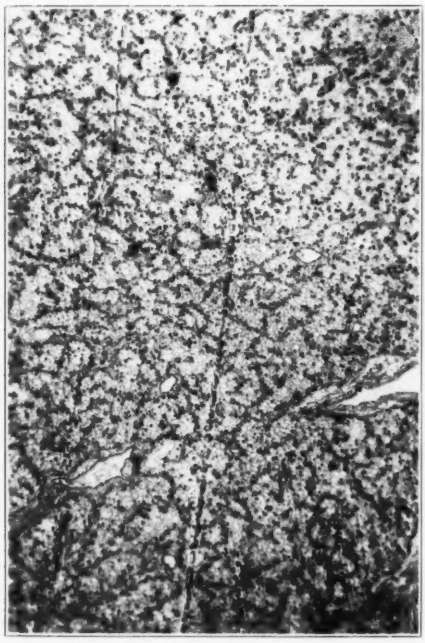

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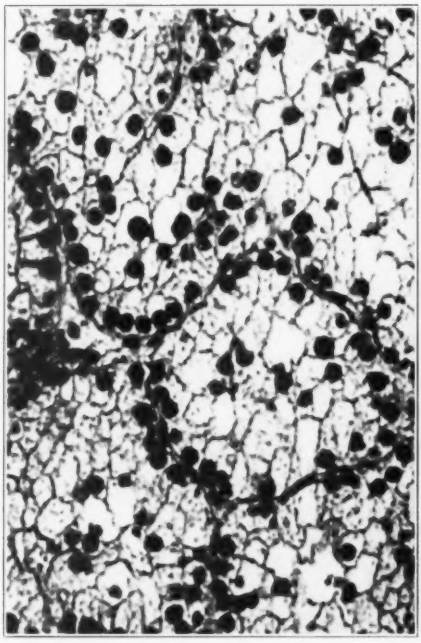

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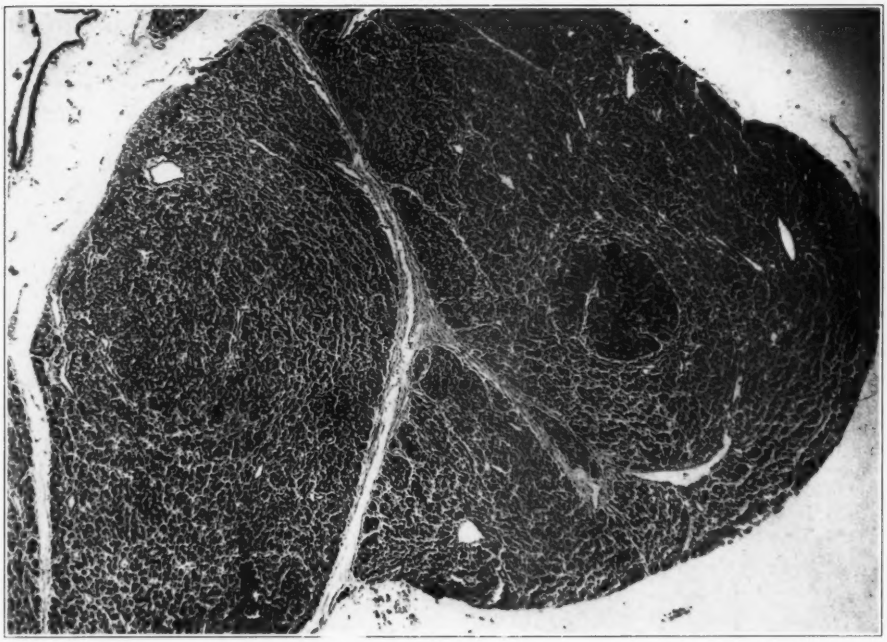
Pathology of Parathyroid Gland

PLATE 4

FIG. 12. Case 23A. A case of parathyroid hyperplasia of the chief cell type. Note the compactness of the cell arrangement, the absence of intercellular fat and the papillary acinar arrangement in one area. × 30.

FIG. 13. A higher power of Fig. 12 taken at the edge of the large circumscribed papillary area, showing the marked basophilism in contrast to the surrounding tissue. × 400.



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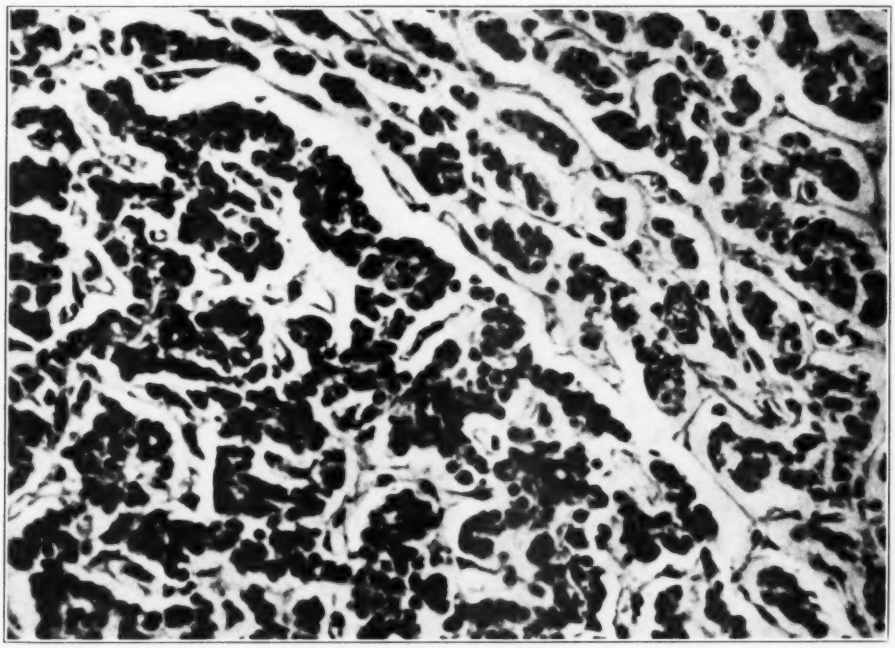

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Castleman and Mallory Pathology of Parathyroid Gland

PLATE 5

FIG. 14. An actual size drawing of the tumors removed from Cases 1 to 11. Note the variability in size and in shape.

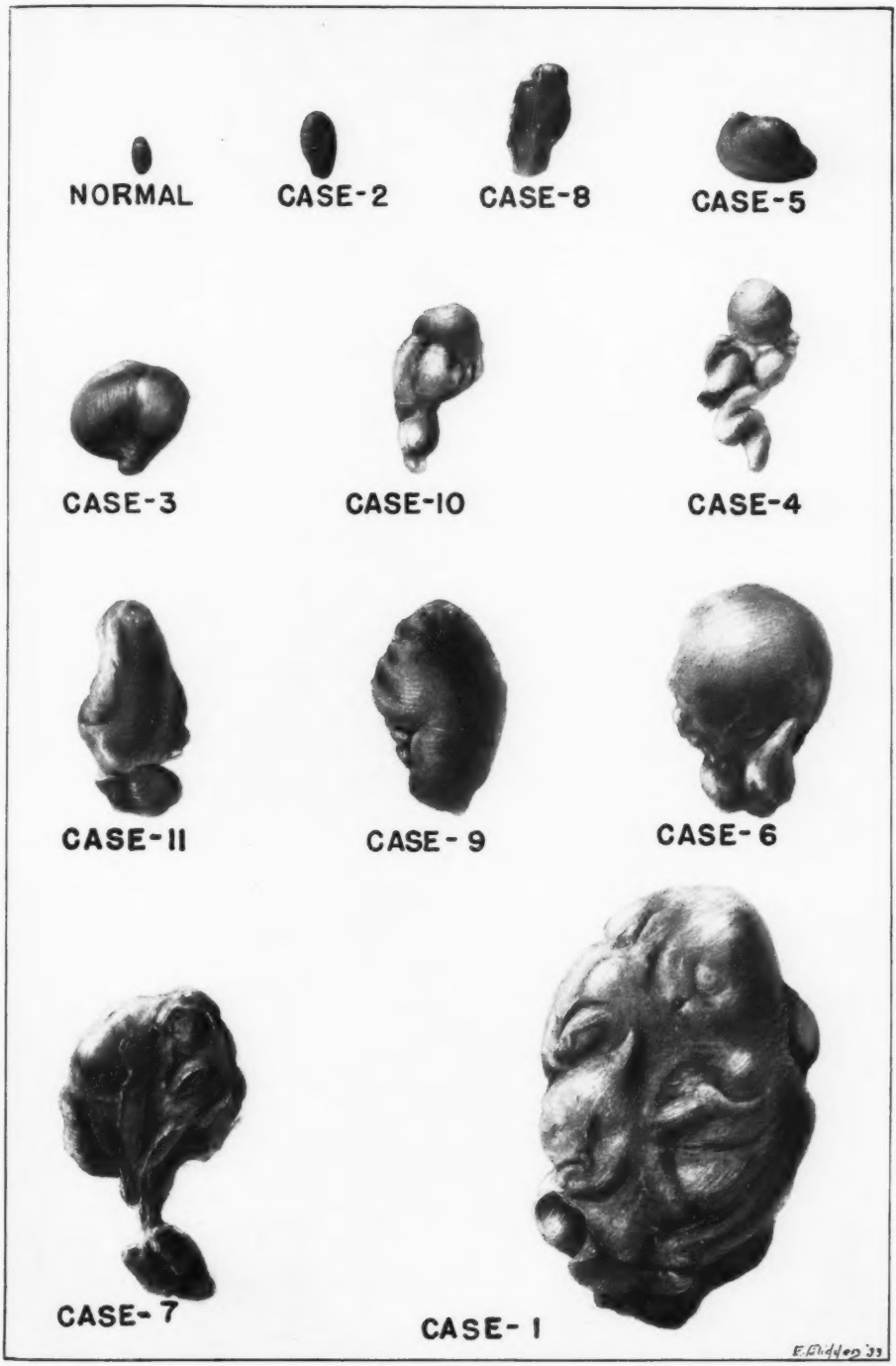
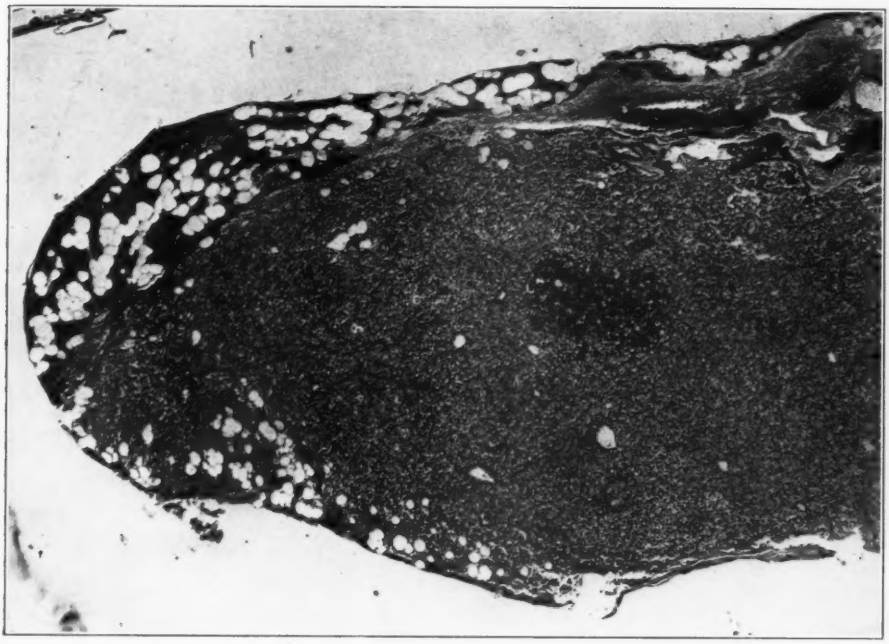

NORMAL
CASE-2
CASE-8
CASE-5
CASE-3
CASE-10
CASE-4
CASE-11
CASE-9
CASE-6
CASE-7
CASE-1

PLATE 6

FIG. 15. Case 2. A longitudinal section through almost the entire tumor showing a rim of normal parathyroid tissue surrounding a wasserhelle adenoma. In the latter is a localized group of transition oxyphil cells. × 15.

FIG. 16. A higher power of Fig. 15, showing the sharply demarcated wasserhelle cell. × 400.



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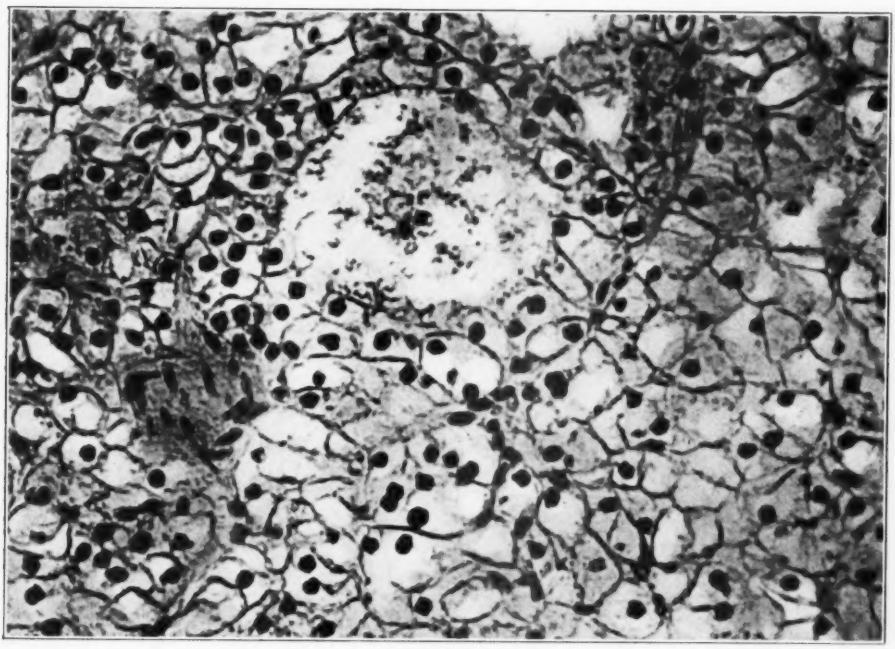

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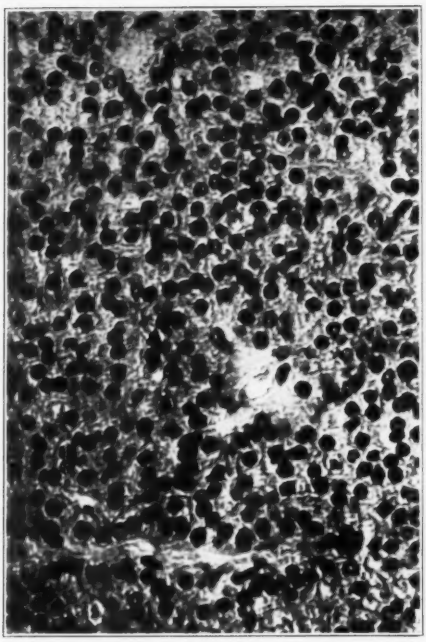
Plate 7

Fig. 17. Case 6. An example of a chief cell tumor showing the enlarged chief cell with its poorly outlined cell margin, its large hyperchromatic nucleus and its faintly acidophilic cytoplasm. Note the increased vascularity, the compact grouping of the cells and the absence of fat. × 400.

Fig. 18. Case 11. A chief cell tumor with numerous greatly enlarged cells and giant hyperchromatic nuclei. Even the smaller cells are well above the normal in size. × 400.

Fig. 19. Case 3. An example of a transition wasserhelle cell tumor. About the nuclei clear halos of varying width can be seen. Occasionally they extend to the cell margins. The cells closely continguous to the stroma are barely discernible. × 400.

Fig. 20. Case 19. An example of a transition oxyphil cell tumor. These cells show transition stages from the chief to the pale oxyphil cell. Note the granular abundant cytoplasm and the pseudoglandular arrangement. × 400.



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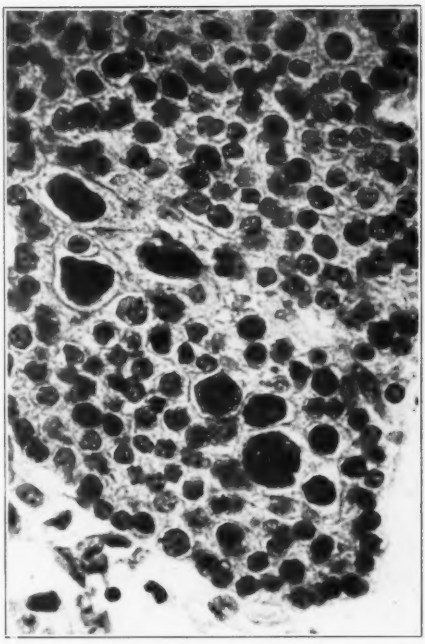

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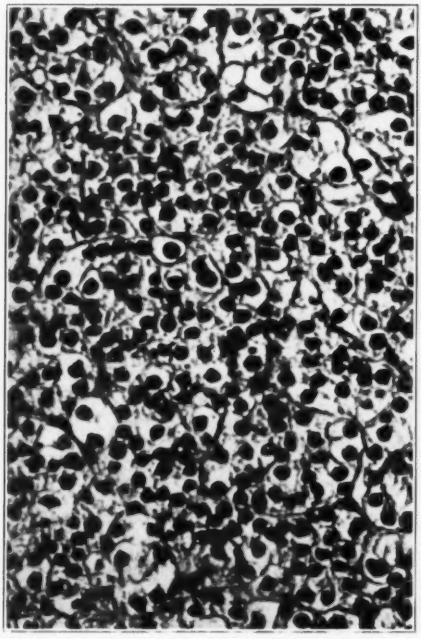

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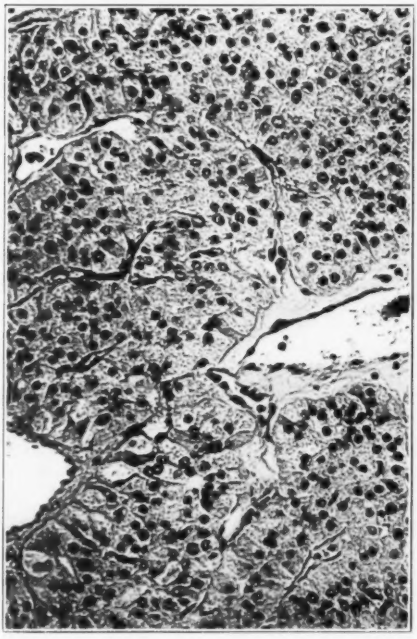

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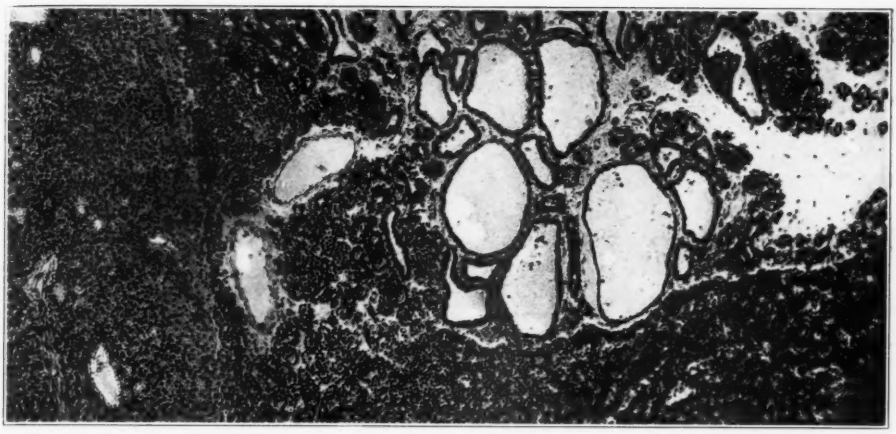
Plate 8

Fig. 21. Case 4. An example of a glandular and cystic chief cell tumor. In addition to the glandular area in the upper part of the photomicrograph note the pale oxyphil cells on the left and the chief cells below. × 50.

Fig. 22. Case 13. Another example of the glandular and cystic type. In this case the spaces are not so close to each other and are larger. Note the presence of red blood cells in some of the glands. × 50.

Fig. 23. Case 13. A higher power of Fig. 22, showing the chief cells lining these spaces. × 400.



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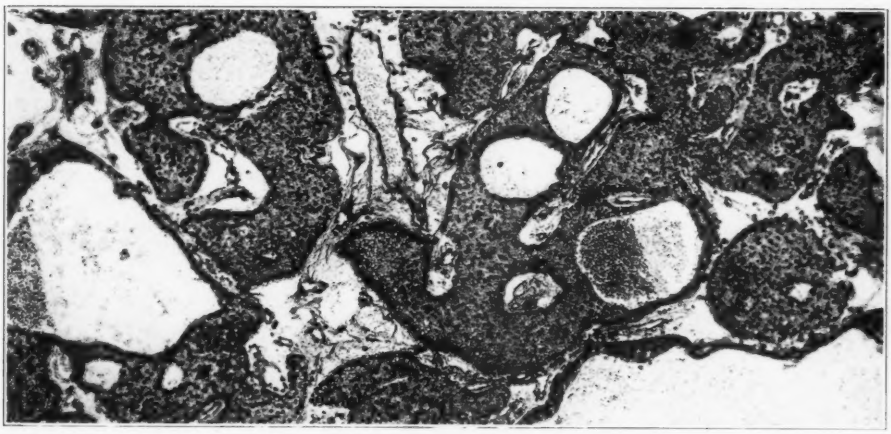

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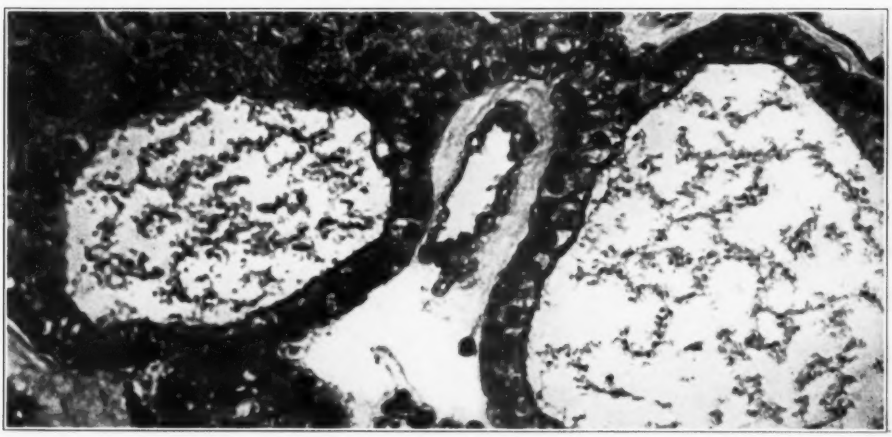

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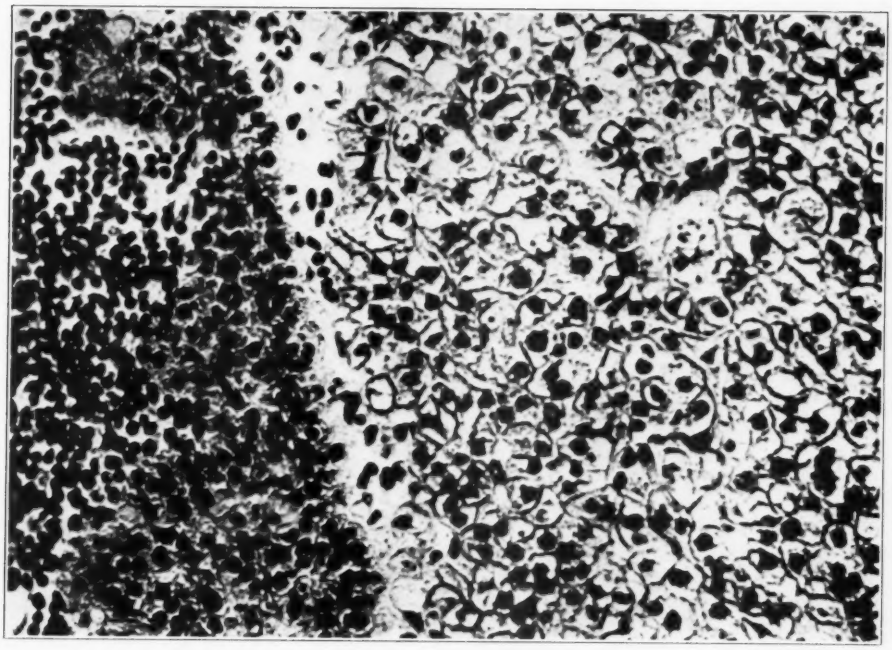
Castleman and Mallory Pathology of Parathyroid Gland

PLATE 9

FIG. 24. An example of a focal wasserhelle cell tumor showing the large islands of waterclear cells, surrounded by moderately enlarged chief cells. × 400.

FIGS. 25 and 26. Case 20. An example of multiple chief cell tumors showing the dissimilarity of two tumors in the same case. One is definitely glandular; the other belongs to the transition wasserhelle cell type and is nonglandular. × 100.



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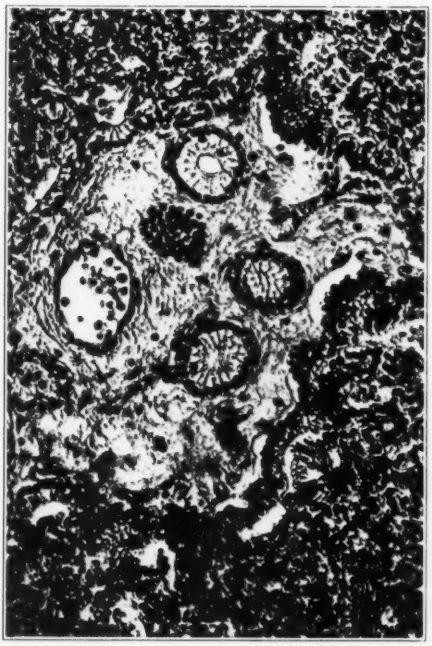

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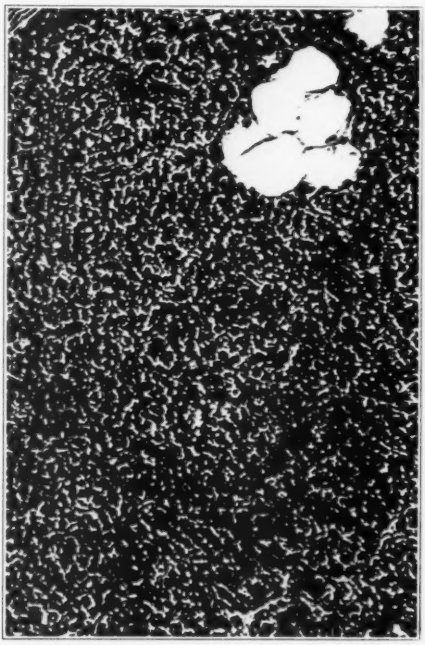

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Castleman and Mallory

Pathology of Parathyroid Gland

ENLARGEMENT OF THE PARATHYROID GLANDS IN RENAL DISEASE*

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The initial impetus to this study was given by a case of typical osteitis fibrosa with adenomatous enlargement of three parathyroid glands and associated polycystic kidneys.† The question which arose in the discussion was in regard to the relation between the kidney disease, obviously congenital in origin, and the parathyroid enlargement.

Since the report by MacCallum,[1] in 1905, of parathyroid adenoma associated with chronic glomerulonephritis, the simultaneous occurrence of renal lesions with parathyroid tumors or enlargement has been noted repeatedly. This association has been emphasized particularly in the recent study of Albright, Baird, Cope and Bloomberg,[2] who collected 83 cases of hyperparathyroidism, 43 of which showed some type of renal damage. The renal lesions are attributed to the precipitation of calcium in the tubules, with resultant sclerosis, contraction and insufficiency, or to the formation of calculi in the pelvis associated with pyelonephritis.

Thus, these authors in general regard the renal lesions as a sequel to the chronic hyperparathyroidism and stress especially the deposition of calcium in the renal tissue as the proximate cause of the kidney lesions. However, in their discussion they raise the question as to whether the parathyroid enlargement may not be secondary to the renal disease in the cases in which multiple glands are affected. They report: "It seems conceivable that a chronic renal insufficiency with phosphate retention and a high inorganic phosphorus level might likewise cause hyperplasia of all parathyroid tissue which might go on to multiple tumor formation. . . . In these cases, the kidney damage may be the cause and not the result of the parathyroid tumors."

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† This case has been reported in detail by Gutman, A. B., Swenson, Paul C., and Parsons, W. B. The differential diagnosis of hyperparathyroidism. *J.A.M.A.*, 1934, **103**, 87 (Case 4, page 90).

Bergstrand [3] in a routine study of the parathyroids in 200 autopsies found a small percentage in which the glands were "distinctly enlarged" and in most of these cases there were at the same time more or less severe changes in the kidneys. Subsequently, a series of nephritis cases was studied: in 10 of 50 cases the combined parathyroid weights exceeded 200 mg., which he regards as the upper limit of normal. We shall refer to these findings again after an analysis of our own data.

Vines [4] in his monograph states: "In chronic nephritis a somewhat similar hyperplasia (*i.e.*, as that in rickets) has been found." He gives no data or references, however.

With this suspicion of a relation between renal disease and parathyroid enlargement before us, it seemed worth while to begin a systematic study, in order to determine whether disease of the kidneys might not lead quite regularly to enlargement of the parathyroids.

Material and Methods

The parathyroid glands in a series of 27 nephritic and 72 miscellaneous cases were dissected out and weighed individually on a Roller-Smith torsion balance, sensitive to 0.2 mg. They were then fixed in Zenker's fluid and sectioned serially for identification and microscopic study. A second series of 29 nephritic and 12 control cases was obtained from neck organs which had been preserved in Klotz or Kaiserling fluid. These glands were also weighed and sectioned. The weights of these fixed specimens were found to be somewhat less than that of the fresh material, but no constant variation was found. The data obtained from this material will therefore be presented separately.

Weights of Parathyroids in Non-Nephritic Cases

In order to have a reliable standard of comparison it was necessary to obtain data on a sufficient number of control cases to show the range of biological variation in comparable groups of individuals. The ideal data for this purpose, as Bergstrand has pointed out, would include only glands from healthy persons who had died suddenly from accidental causes. Such material was not available, and we have been forced to take as controls the weights of glands from non-nephritic patients dying of various diseases. Knowing nothing of the effect which such diseases might have upon the parathyroids, it cannot be assumed that these weights represent "normal" values in a strict sense, but for the purpose of our inquiry, namely to ascertain if nephritis is commonly associated with parathyroid enlargement,

they would seem to provide a sufficiently accurate standard of comparison. So, also, a calculation of the amount of functional parenchyma would have to take into account the relative amount of interstitial fat and fibrous tissue. No attempt has been made to correct for this variable, since there seems to be no simple method for so doing, and in the comparison of fairly large numbers the error introduced by neglecting this would not appear to be significant.

The literature contains surprisingly few systematic studies of the weights of the human parathyroid. The available references to parathyroid weights in adults are given in tabular form (Table I).

TABLE I

Weights of Parathyroid Glands Cited from Literature

Author	Year	Mean weight		Combined weight
		Upper	Lower	
		gm.		*gm.*
Welch [5]	1898	0.035		
Marañon [6]	1911	0.020–0.050		0.080–0.120
Danisch [7]	1924	0.026–0.030	0.037–0.041	
Marine [8]	1928	0.020	0.035	
Aibara [9]	1931			0.067

Bergstrand,[3] 1921, gives as the upper limit of normal combined weight 200 mg., a figure which on the basis of our own data seems considerably in excess of normal. The weights which we have obtained in our series of non-nephritic control cases in which the kidneys showed no microscopic lesions of significance are presented in Table II.

These data are summarized in Table III, which gives also the standard deviation and the probable error of the mean. These figures are in close agreement with those of Danisch.

INFLUENCE OF SEX ON THE WEIGHT OF NORMAL PARATHYROIDS

It is evident from the table that the mean weights of each gland in the female exceeds that of the male. In the case of the right upper, right lower, and left upper, the difference is statistically significant.

TABLE II

Weights of Parathyroid Glands in Cases with Normal Kidneys

Autopsy No.	Age	Sex	Right upper	Right lower	Left upper	Left lower	Combined weights	Principal diagnosis
	yrs.		*gm.*	*gm.*	*gm.*	*gm.*	*gm.*	
11,392	54	F		0.058	0.026			Bacteremia, hemolytic staphylococcus
11,393	31	F	0.035	0.032	0.025	0.031	0.123	Chorionic carcinoma
11,394	42	M		0.014				Glioblastoma
11,402	56	M	0.024	0.030	0.029			Carcinoma of rectum
11,403	64	M			0.016			Carcinoma of urethra
11,404	51	M	0.094		0.069		0.163	Lobar pneumonia, amebic colitis
11,405	55	M		0.025		0.027		Lobar pneumonia
11,406	29	F	0.021			0.031		Bacteremia, hemolytic staphylococcus
11,410	58	F	0.026		0.019	0.018		Epithelioma of uterus
11,411	60	M	0.016	0.019	0.015	0.025	0.075	Abdominal aneurysm, arteriosclerosis
11,413	41	F		0.059	0.038	0.019		Pylephlebitis
11,415	50	M	0.036		0.029	0.050		Endarteritis obliterans
11,419	25	F	0.036		0.041	0.035		Subacute bacterial endocarditis
11,423	50	F	0.022		0.041	0.016		Sepsis after hysterectomy
11,425	74	M	0.025		0.035	0.037		Arteriosclerosis
11,427	58	F	0.048	0.047				Lobar pneumonia
11,431	47	M	0.017	0.031	0.018	0.027	0.093	Emphysema
11,435	40	F	0.029	0.066	0.038	0.034	0.167	Syphilitic aneurysm of aorta
11,436	26	M	0.026	0.029		0.030		Lymphoepithelioma of pharynx
11,438	64	F	0.039					Aneurysm of abdominal aorta
11,440	44	M	0.017	0.022	0.037			Abscess of brain
11,441	67	M	0.047	0.036	0.050	0.040	0.173	Aneurysm of cerebral artery
11,447	42	F	0.062	0.058	0.031			Acute appendicitis with perforation
11,449	74	M			0.006			Carcinoma of stomach
11,450	14	M	0.012			0.013		Rheumatic heart disease
11,460	55	M	0.013	0.016				Arteriosclerosis
11,461	52	M	0.011	0.042	0.034	0.031	0.118	Rheumatic heart disease
11,463	75	F	0.026	0.027	0.020	0.034	0.107	Carcinoma of gall-bladder
11,464	40	M	0.024	0.023	0.024			Chronic ulcerative colitis
11,470	53	M	0.034		0.028	0.029		Congenital heart disease
11,471	77	F	0.021	0.022	0.015	0.021	0.079	Carcinoma of breast
11,472	13	F	0.028	0.029	0.031	0.040	0.128	Acute leukemia
11,475	74	F	0.018		0.043	0.032		Carcinoma of gall-bladder

11,476	33	M	0.017	0.010	0.014	0.007	0.048	Hodgkin's disease
11,477	38	F	0.024	0.019	0.011	0.017	0.071	Encephalomyelitis
11,479	28	M	0.021	0.037		0.015		Meningoencephalitis
11,480	64	M	0.046	0.037	0.031	0.009	0.123	Multiple myeloma
11,481	58	M	0.019	0.009	0.015	0.027	0.070	Bacterial endocarditis
11,482	40	F	0.026	0.051	0.026			Carcinoma of breast
11,487	53	M	0.029	0.044	0.023	0.035	0.131	Thrombosis of femoral veins
11,489	70	M	0.019		0.020	0.013		Carcinoma of esophagus
11,491	62	M	0.013	0.016	0.010	0.031	0.070	Rheumatic endocarditis
11,492	67	F	0.023	0.023	0.024	0.042	0.112	Sarcoma of antrum
11,494	62	M	0.030	0.035	0.031	0.022	0.118	Arteriosclerosis
11,495	64	M	0.030	0.065	0.007	0.037	0.139	Duodenal ulcer
11,500	71	M	0.015	0.014	0.008	0.022	0.059	Generalized arteriosclerosis
11,502	67	M	0.029	0.044	0.051	0.067	0.191	Duodenal ulcer
11,505	51	M	0.089		0.033	0.046	0.168	Rheumatic heart disease
11,511	34	F	0.011		0.015	0.027		Pneumonia
11,514	25	M	0.032	0.017	0.020	0.028	0.097	Abscess of brain
11,517	14	M	0.025	0.021	0.028	0.023	0.097	Generalized miliary tuberculosis
11,518	32	M	0.023	0.025	0.025	0.038	0.111	Carcinoma of sigmoid colon
11,519	50	M	0.028	0.040	0.033	0.049	0.150	Carcinoma of sigmoid colon
11,520	23	M			0.025	0.025		Lymphatic leukemia
11,523	52	M	0.022	0.026	0.014	0.040	0.102	Carcinoma of rectum
11,526	58	M	0.009		0.018	0.028		Lobular pneumonia
11,528	81	M	0.017	0.023		0.032		Carcinoma of prostate
11,529	38	F		0.035	0.017	0.055		Acute pancreatitis
11,530	42	F	0.072	0.058	0.112	0.056	0.298	Tetanus
11,533	33	F	0.038	0.040	0.048	0.020	0.146	Tuberculous meningitis
11,535	44	F	0.047	0.046	0.026	0.042	0.161	Hemolytic streptococcus sepsis
11,536	36	F	0.030	0.014	0.029	0.028	0.101	Rheumatic carditis
11,538	48	F	0.017	0.028	0.018	0.022	0.085	Lymphosarcoma of stomach
11,539	82	M	0.041			0.045		Senile arteriosclerosis
11,544	46	M	0.021	0.021		0.030		Hodgkin's disease
11,545	25	F	0.035	0.032	0.021	0.049	0.137	Cystadenoma of ovary
11,546	60	F	0.040		0.043			Carcinoma of ampulla of Vater, acute pancreatitis
11,547	56	F	0.009	0.025	0.015	0.032	0.081	Acute streptococcus sepsis following angina
11,548	33	F	0.036	0.020	0.022	0.053	0.131	Lymphogranulomatosis inguinalis (rectal)
11,557	57	M	0.014		0.011	0.021		Carcinoma of stomach
11,559	49	M	0.018	0.028	0.015	0.024	0.085	Lead poisoning, thrombosis
11,561	48	M	0.015	0.023	0.020	0.015	0.073	Rheumatic endocarditis, ulcers of duodenum

The calculated total parathyroid weight for males is 0.106 gm. and for females 0.130 gm. The glands from females are thus approximately 20 per cent heavier. If it had been possible to take into consideration the relation to total body weight the difference might have been still greater.

The explanation of this sex difference is not immediately apparent. It does not appear to be correlated with repeated pregnancies. The

TABLE III

Mean Weights of Parathyroid Glands in Non-Nephritic Cases

Gland	No. of cases	Mean weight	Standard deviation
		gm.	gm.
Right upper	62	0.027 ± 0.0013	0.013
Right lower	51	0.032 ± 0.0013	0.014
Left upper	59	0.027 ± 0.0013	0.015
Left lower	58	0.031 ± 0.0010	0.012
Combined weight (calculated)			0.117
Combined weight (observed, 37 cases)			0.118

mean weights of the glands in nulliparas are if anything slightly in excess of those in women who have borne children.

On the other hand, if the weights of the glands in women before and after the menopause (arbitrarily taken as 45 years) be calculated separately, the increased mean weight is found to lie entirely in the younger group. This is shown in Table V.

Although the differences in the two groups are not sufficiently great to be statistically significant, except in the case of the left lower, they are consistent for each gland and probably represent a true difference. A similar analysis of the weights of the male glands discloses no comparable difference in the two age groups. The inference which is suggested, if not proved by our data, is that the age period of sexual activity in females is marked by a definite increase in the weight of the parathyroid.

TABLE IV

Influence of Sex on Weight of Normal Parathyroids

	Right upper		Right lower		Left upper		Left lower		Combined weight (calculated)
	No. of cases	Mean weight	No. of cases	Mean weight	No. of cases	Mean weight	No. of cases	Mean weight	
		gm.		*gm.*		*gm.*		*gm.*	*gm.*
Males	36	0.027 ± 0.0011	30	0.027 ± 0.0015	33	0.023 ± 0.0013	35	0.029 ± 0.0010	0.106
Females	26	0.031 ± 0.0006	21	0.037 ± 0.0008	26	0.030 ± 0.0008	23	0.032 ± 0.0012	0.130
Per cent increase females over males		15		37		30		10	22

TABLE V

Mean Weights of Parathyroids in Females Under and Over 45 Years of Age

Age	Right upper		Right lower		Left upper		Left lower		Combined weight (calculated)
	No. of cases	Mean weight	No. of cases	Mean weight	No. of cases	Mean weight	No. of cases	Mean weight	
yrs.		*gm.*		*gm.*		*gm.*		*gm.*	*gm.*
Under 45	15	0.035 ± 0.0026	14	0.040 ± 0.0029	16	0.033 ± 0.0038	15	0.036 ± 0.0022	0.144
Over 45	11	0.026 ± 0.0027	7	0.033 ± 0.0033	10	0.026 ± 0.0023	8	0.027 ± 0.0020	0.112
Per cent increase		35		21		27		33	29

Relation of Parathyroid Weight to Age

Taking the series as a whole no correlation has been found between the weight of the parathyroids and the age. This is brought out in Table VI.

While the numbers in each group are too few to permit of statistical analysis, it is evident that there is no definite trend either toward an increase or decrease with advancing age. It should be noted that our data include no cases below the age of 10 and only 3 in the 10–19 year old group.

Weights of Parathyroids in Nephritic Cases

This group may be analyzed first from the point of view of the pathological lesions. The parathyroids were obtained from 27 cases in which at autopsy there were found significant lesions in the kidneys. The data are given in Table VII.

A summary showing in tabular form the mean weights together with the PE_M in the renal cases is given in Table VIII.

Thus, in an unselected series of cases with renal lesions there is found an increase in the weights of the parathyroid as compared with those of a control series. This applies to the individual groups as well as to the total combined weights. This difference is slightly less than three times the square root of the sums of the squares of the probable errors of the means in the cases of the right upper, right lower, and left upper, and slightly greater than three times in the cases of the left lower parathyroids. Strictly, the data are statistically significant only in this last group, according to accepted usage. But the probability that the increased weight in the renal cases is not accidental is enhanced by the fact that it is seen in each comparable group.

Since this series includes indiscriminately various types of renal lesions of various degrees of severity, without regard to duration or to clinical evidence of renal insufficiency, it is probable that the mean differences between the two groups are correspondingly reduced.

Assuming that the increased mean weight of the parathyroid is significant, the question arises as to whether it is due to the inclusion of a few glands of abnormal size or to a general tendency to enlargement. In Chart I are shown distribution curves for the weight of the

TABLE VI

Weights of the Parathyroids at Various Ages

Age	Right upper		Right lower		Left upper		Left lower		Combined weight (calculated)
	No. of cases	Mean weight	No. of cases	Mean weight	No. of cases	Mean weight	No. of cases	Mean weight	
yrs.		*gm.*		*gm.*		*gm.*		*gm.*	*gm.*
10–19	3	0.022	2	0.025	2	0.030	3	0.025	0.102
20–29	6	0.029	4	0.039	4	0.026	7	0.030	0.124
30–39	8	0.027	8	0.024	9	0.023	9	0.031	0.105
40–49	12	0.031	14	0.038	12	0.034	9	0.030	0.133
50–59	15	0.023	11	0.033	15	0.025	14	0.032	0.113
60–69	10	0.031	8	0.033	10	0.028	8	0.032	0.124
Over 70	8	0.026	4	0.022	7	0.021	8	0.030	0.099

TABLE VII

Weights of Parathyroid Glands in Cases with Renal Lesions

Autopsy No.	Age	Sex	Right upper	Right lower	Left upper	Left lower	Combined weight	Type of renal lesion	Marked renal insufficiency
	yrs.		*gm.*	*gm.*	*gm.*	*gm.*	*gm.*		
11,459	15	F	0.037	0.052	0.060	0.082	0.231	Chronic glomerulonephritis	+
11,456	21	M	0.077		0.041	0.040		Subacute glomerulonephritis	+
11,486	43	M	0.025	0.052	0.051	0.050	0.178	" "	+
11,378	44	F	0.022		0.013			Embolic glomerulonephritis	
11,474	27	M	0.041	0.058	0.035	0.033	0.167	" "	
11,504	35	M	0.044	0.030	0.033	0.035	0.142	" "	
11,516	40	M			0.026	0.031		Acute glomerulonephritis	+
11,399	38	M	0.038	0.196	0.051	0.148	0.433	Advanced pyelonephritis and renal calculi	+
11,485	29	F	0.042		0.031	0.035		Pyelonephritis and calculus (left)	
11,390	54	M			0.056			Arteriolar nephrosclerosis	
11,453	69	F		0.047		0.074		" "	
11,396	46	M	0.033		0.035			" "	+
11,400	37	F	0.248	0.016				" "	+
11,424	49	F	0.037		0.046			" "	
11,455	58	M				0.039		" "	
11,553	66	M	0.062	0.065	0.029	0.038	0.194	" "	+
11,556	43	F	0.043		0.040	0.027		" "	
11.462	60	F	0.025	0.013	0.035	0.020	0.093	" "	
11,398	72	F	0.053	0.034	0.010	0.056	0.153	Arteriosclerotic scars	
11,484	36	F	0.014	0.016	0.014	0.023	0.067	" "	
11,496	49	M	0.067					" "	
11,420	43	F	0.009	0.036	0.020			Slight hydronephrosis	
11,437	47	M		0.046	0.030	0.033		Marked hydronephrosis	+
11,434	59	M	0.013	0.051	0.032	0.067	0.0163	Chronic interstitial nephritis	
11,488	72	F			0.028			Infarcts of kidneys	
11,453	35	F	0.031		0.017	0.045		Healed infarcts	
11,490	54	M	0.031	0.041		0.026		Calculus, nephrectomy (right)	

TABLE VIII

Mean Weights of Parathyroids in Nephritic and Non-Nephritic Cases

Cases	Right upper		Right lower		Left upper		Left lower		Combined weight (calculated)
	No. of cases	Mean weight	No. of cases	Mean weight	No. of cases	Mean weight	No. of cases	Mean weight	
		gm.		*gm.*		*gm.*		*gm.*	*gm.*
Nephritic	21	0.047 ± 0.0069	15	0.050 ± 0.0074	22	0.033 ± 0.0018	19	0.047 ± 0.0044	0.177
Non-nephritic	62	0.027 ± 0.0011	51	0.032 ± 0.0013	59	0.027 ± 0.0013	58	0.031 ± 0.0011	0.117
Per cent increase in nephritics		74		56		22		47	50

TABLE IX

Mean Weights of Parathyroids in Cases with Severe Renal Insufficiency

Cases	Right upper		Right lower		Left upper		Left lower		Combined weight (calculated)
	No. of cases	Mean weight	No. of cases	Mean weight	No. of cases	Mean weight	No. of cases	Mean weight	
		gm.		*gm.*		*gm.*		*gm.*	*gm.*
Severe nephritis	7	0.072	5	0.072	8	0.042	7	0.059	0.244
Controls	62	0.027	51	0.032	59	0.027	58	0.031	0.117
Per cent increase		166		125		56		90	109

glands in the series of nephritic and non-nephritic cases. Because of the relatively small number of nephritic cases the curves are irregular, but it is clearly seen that the greater percentage of the nephritic cases falls to the right of the mode of the controls. Of the right upper glands, 71 per cent exceed the mean weight of the controls; of the right lower, 73 per cent; of the left upper, 73 per cent; of the left lower 74 per cent. In 10 cases in which all four glands were recovered, the total weight exceeded the mean total weight of the controls (118 mg.) in 8. The 2 cases in which the total weight was lower showed only arteriosclerotic scars without clinical evidence of renal insufficiency. Of the 8 cases which were above the normal mean 4 had all glands above the mean and 4 showed enlargement of three glands, indicating that the overgrowth is not limited to one or two of the glands in a given case.

The conclusion which seems justified from this analysis is that the parathyroid enlargement is the expression of a general trend and that the increase in mean weight in the nephritic series is not due to the inclusion of a few glands of exceptional size.

In view of the fact that the female glands average heavier than the males, it should be pointed out that the nephritic series includes 14 males and 13 females. The mean of the male parathyroid is larger than that in the females. It is therefore improbable that the normal sex difference is a factor in the enlargement found in the nephritic cases.

Thus far the discussion has concerned unselected cases of renal disease without regard to the intensity of the lesions or their character. It was of interest to ascertain if there existed a correlation between the degree of parathyroid enlargement and the severity or character of the kidney disease.

Reference to Table VII shows that the maximum enlargement occurred in 2 cases of suppurative nephritis and pyelonephritis in which the combined weight of the parathyroids was approximately four times the normal. The next degree of enlargement was in the 3 cases of subacute and chronic glomerulonephritis, in 2 of which the combined weight of the four glands was approximately double the normal. Lesser increases in weight were found in the nephrosclerotic and other types. In those cases in which the renal lesions were unilateral, acute or focal in character, no enlargement of the parathyroids was found.

An attempt has been made to correlate the degree of enlargement with the severity of the clinical symptoms. From the group of 27 cases showing pathological changes in the kidneys we have selected 9 in which the clinical record gave evidence of severe renal insufficiency.

Comprised in this group are 4 cases of chronic and subacute glomerulonephritis (11,459, 11,456, 11,486), 1 of which (11,399)

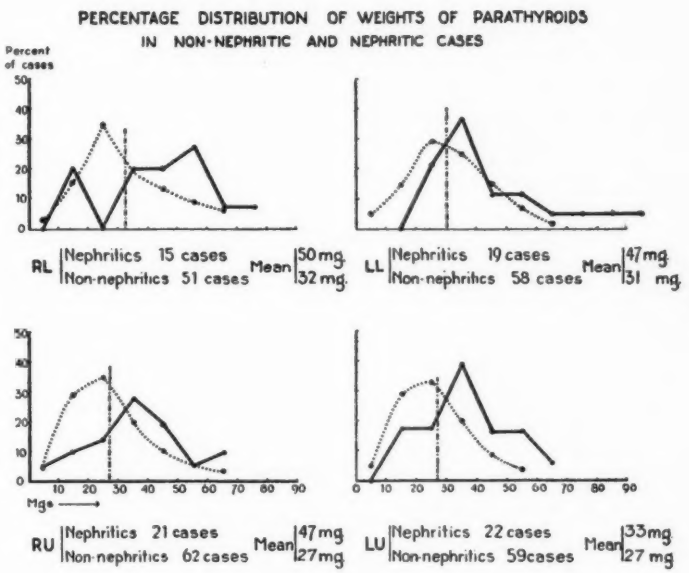

CHART 1

also had a renal calculus and pyonephrosis (all died with uremic symptoms); 3 cases of arteriolar nephrosclerosis with hypertension and terminal uremia (11,396, 11,400, 11,556); 1 marked hydronephrosis (11,437) following carcinoma of the bladder with uremia; and 1 case of acute glomerulonephritis (11,516). In spite of the smallness of the series there is rather convincing evidence that the enlargement of the parathyroids is correlated with the severity of the clinical picture. The number of cases in each group is too small and the variations too wide to justify statistical analysis.

Data on Fixed Specimens

As confirmatory evidence for the frequent association between parathyroid enlargement and renal disease we may supplement the above findings with data based on the weights of glands obtained from museum specimens. They can be presented most briefly in tabular form (Table X).

Although the actual weights of the glands are reduced by the fixation to about 70 per cent of the unfixed organs, a relative increase in weight is again found in the nephritic series, as compared with the controls. This increase is statistically significant for each group of glands in the severe cases and for the right lower and left upper in the series without clinical evidence of severe nephritis. Since these data merely confirm the observations on unfixed material, it is unnecessary to consider the cases individually.

Histological Changes

The material at hand does not lend itself to detailed cytological study. The primary purpose in sectioning glands was to make sure that no lymphatic or tissue other than parathyroid was included in the weighing. Only a few tentative statements can therefore be made in comparing the histology in the nephritic and non-nephritic cases. In spite of great variability, the impression is obtained that the glands of nephritic cases show a more compact structure and relatively less interstitial adipose tissue than those of the control series. Furthermore, the dominant cell type in most of the "nephritic" glands is the large water-clear cell in which the juxtanuclear body appears conspicuously. Oxyphile cells are not more numerous than in the control glands and indeed seem unusually sparse in some of the nephritic cases.

Definite adenomas were found three times in the nephritic series and twice in the control. They were all of the oxyphile cell type. Further study is needed to determine whether the enlargement of the glands in nephritis is due to hypertrophy of individual cells or to increase in their number.

There have been few systematic studies of the histology of the parathyroid in nephritics. Koopmann [10] examined 5 cases of chronic renal disease, including malignant nephrosclerosis, chronic glomerulonephritis, and a case of cystic disease. No histological

TABLE X

Mean Weights of Parathyroids in Nephritic and Control Cases, Based on Fixed Museum Specimens

Classification	Right upper		Right lower		Left upper		Left lower		Combined weight (calculated)
	No. of cases	Mean weight	No. of cases	Mean weight	No. of cases	Mean weight	No. of cases	Mean weight	
		gm.		*gm.*		*gm.*		*gm.*	*gm.*
Severe nephritis with renal insufficiency	12	0.039 ± 0.0044	8	0.052 ± 0.0070	11	0.031 ± 0.0024	9	0.042 ± 0.0036	0.164
Per cent increase over normal		77		108		72		68	82
Renal lesions without clinical nephritis	17	0.027 ± 0.0029	13	0.038 ± 0.0035	14	0.032 ± 0.0018	8	0.037 ± 0.0038	0.134
Per cent increase over normal		23		52		78		48	49
Miscellaneous controls	12	0.022 ± 0.0026	10	0.025 ± 0.0026	9	0.018 ± 0.0008	10	0.025 ± 0.0018	0.090

changes were found which could be correlated with the renal lesions or interpreted as indicating hyper- or hypofunction. No weights or measurements are given.

Radnai [11] also has studied the parathyroids in 20 nephritic cases and 20 controls of similar age groups. He believes that there is a somewhat earlier appearance of oxyphile cells and in greater number in the nephritic cases, but finds no other characteristic change. No weights or measurements are given.

Discussion

The principal facts which have emerged from this study are: (1) the mean weight of the female parathyroid glands is greater than that of males; (2) the mean weight of the parathyroids is significantly increased in any type of nephritis, if the lesions are diffuse and severe. We shall discuss briefly the possible implications of these findings.

The sex difference in the weights of the parathyroids has, so far as we are aware, not been previously observed. The first explanation that comes to mind is that the loss of calcium due to pregnancy or lactation might increase the functional demands upon the parathyroids and lead to their enlargement. Our data do not support this theory, since the enlargement was even more marked in nulliparas than in women who had borne children.

Another possibility is that the increased parathyroid weight may be in some as yet obscure way correlated with the alterations of the anterior lobe of the hypophysis which accompanies the menstrual cycle (Andersen[12]). It has been shown recently by Anselmino, Hoffmann and Herold [13] that injection of anterior pituitary lobe extract in rats is followed by a rapid hypertrophy of the parathyroids, with a characteristic change in the cytological picture. Hertz and Kranes [14] have reported similar effects in rabbits. Whether this is a reversible change or not is not known; nor has it been demonstrated yet that this activity of the anterior lobe is due to a special hormone. It is obvious that the exact explanation for the sex difference in parathyroid weights in humans must await further experimental study.

Our observations have brought out clearly the fact that most, if not all, cases of diffuse renal disease are accompanied by a significant

enlargement of the parathyroid glands. Since this occurs in such varied types of renal disorders as glomerulonephritis, arteriolar nephrosclerosis, hydronephrotic atrophy and suppurative pyelonephritis there must be some common chemical factor that stimulates the parathyroids to increased activity and growth.

It seems hardly justified to enter upon an extended discussion of the nature of this correlation on the basis of the data here presented. It is probable that the cases with severe clinical nephritis had phosphate retention, and since "any increase in PO_4 ions will decrease the amount of Ca ions in the blood" (Thomson and Collip[15]), this may incite the parathyroids to increased activity and overgrowth. Whether this simple explanation is adequate or not must be determined by further clinical and experimental studies; our data include only a few determinations of inorganic PO_4 and Ca in the nephritic series, and no conclusions as to a positive correlation can be drawn from them.

It is interesting that the group of cases in which renal lesions were found at autopsy, but in which symptoms of renal insufficiency were not recognized, nevertheless showed in most cases a certain degree of parathyroid enlargement.

It is unfortunate that the bones in this series of nephritic cases could not be carefully studied. Although in none of the cases was there any clinical or gross pathological suspicion of bone disorder, it is possible that those cases in which the parathyroid enlargement was most pronounced might have shown microscopic lesions indicating increased resorption. In renal dwarfism, in which the kidney disease leads often to extreme rickets-like deformity of the skeleton, the parathyroids have not been carefully studied. Langmead and Orr,[16] however, have reported a case in which there did occur parathyroid enlargement and they suggest that the bone changes may have been due in part to excessive parathyroid activity. It may indeed be true that excessive activity of the parathyroids during the growth period may bring about more severe skeletal deformities than in adult life.

In the series of cases which we have analyzed it seems obvious enough that the diverse renal lesions could not have resulted from excessive functional activity of the parathyroids. In the group of cases of hyperparathyroidism collected by Albright, Baird, Cope and Bloomberg [2] it is taken for granted that the renal lesions found in

over half the cases are attributable to the excessive activity of the parathyroids, and in large measure are due to calcium deposition. They hold that the precipitation of calcium phosphate in the renal parenchyma eventually leads to inflammatory changes, sclerosis and contraction, which simulate both chronic glomerular and vascular nephritis. We believe that few pathologists would accept this without question. In some of the cases cited the deposition of calcium in the renal tissues may well have been due to the hyperparathyroidism, and may have been entirely unrelated to a preëxisting nephritis. It is possible, then, that a certain proportion of cases of so-called hyperparathyroidism may be initiated by chronic renal disease.

Summary

1. The mean weights of the parathyroid glands in a series of miscellaneous non-nephritic cases over the age of 10 years is 27 mg. for the upper parathyroid and 31–32 mg. for the lower. The mean combined weight is 118 mg.

2. In the male glands there is no change correlated with advancing age.

3. In the female gland there was found an increase in weight of approximately 22 per cent during the active sexual period; after 45 years there is a decline of weight to figures corresponding with those of the series as a whole. The enlargement is not correlated with pregnancy.

4. The mean weight of the parathyroids in various types of chronic renal disease exceeds that of non-nephritic cases. In an unselected series this increase in mean weight is approximately 50 per cent; in cases with advanced renal lesions the increase amounts to more than 100 per cent.

5. The increase in weight of parathyroids is roughly proportional to the severity and extent of the renal lesions and to the intensity of the clinical signs of renal insufficiency. Usually three or four of the glands share in the enlargement.

Note: We desire to express our thanks to Dr. Walter W. Palmer and to Dr. Allen O. Whipple for permission to utilize the clinical records in these cases.

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ATYPICAL AMYLOID DISEASE*

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The following cases of extensive amyloid disease are reported because they possess several unusual features. Suppuration, tuberculosis and malignancy with infection were absent in all. Primary amyloid disease, so-called because of the absence of any known etiological factor, is a rare condition and only a few cases have been reported in the literature.

Of 1500 autopsies performed at the Montefiore Hospital during the past 7 years 112 showed evidence of amyloid disease; 100 of these were associated with pulmonary tuberculosis. This represented 25 per cent of all patients dying with this disease. Of the 12 cases of amyloidosis in patients dying with diseases other than pulmonary tuberculosis 3 had no apparent etiological factor, 2 were associated with carcinoma of the lung and secondary suppuration, 1 was associated with chronic osteomyelitis, 3 with pyelonephritis, 1 with carcinoma of the stomach, 1 with leukemia, and 1 with tabes dorsalis. The more unusual of these cases are reported in this communication.

Lubarsch,[1] in a discussion of atypical amyloid deposition, noted certain characteristics of this group of cases. (1) There is almost complete absence of amyloid in those organs that are most involved in ordinary amyloidosis (liver and spleen). (2) Organs such as the heart and lungs, the skin and striated muscle, not affected generally in amyloidosis, are particularly involved. (3) The amyloid may occur in the form of discrete nodules (Eppinger's case). (4) Frequently the deposits fail to react to the well known tests for amyloid. (5) There is no demonstrable concomitant infection such as is found in the typical amyloidosis.

Lubarsch reported 3 cases of atypical amyloidosis. (1) A case of chronic endocarditis of the mitral valve in which amyloid deposits were found in the heart, lung, stomach, esophagus, small and large intestine and skin. In this case there was, however, a mild

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ascending genito-urinary infection. (2) A male 53 years of age with symptoms and signs of scleroderma, myotonia and marked macroglossia, which was diagnosed as carcinoma of the tongue. This proved to be due to massive amyloidosis of the tongue. (3) A male 45 years of age with multiple ulcerations of the stomach, hemorrhagic cystitis with marked amyloidosis of the spleen, trachea, bronchial and mesenteric lymph nodes, prostate, seminal vesicles, epididymis, testes, stomach, heart muscle and lungs. The only suppuration or infection was an antecedent gonorrhea which had completely disappeared.

Recently Gerstel[2] reported a case of diffuse amyloidosis in a female 52 years of age who, after the use of a denture, observed swelling of the floor of the mouth. The tongue became so large that she could not close her mouth. A sarcoma of the tongue was suspected. The entire tongue was hard and swelling extended to the neck. The patient became progressively weaker and during the 3 months preceding death developed increasing dyspnea, edema of the lower extremities and severe diarrhea. Examination revealed an emaciated woman with generalized anasarca. Her lids were swollen and yellowish brown. At autopsy diffuse amyloidosis was found involving the tongue, skin of the neck, esophagus, pylorus, intestine, heart and adventitia of large vessels. There was no evidence of inflammation in any of the organs and no definite cause could be found to account for the amyloidosis. The striking features of the case were the rapidity of the development of the amyloid of the tongue, resulting in death in 2 years, and the unusual dysentery-like symptoms due to amyloid of the gut.

Pick,[3] in discussing amyloid disease, mentioned a case of a man of 54 years who, 8 years prior to his death, developed symptoms of difficulty in digestion and deglutition and progressive difficulty in moving the tongue. At autopsy widespread amyloid of the musculature was found, particularly of the tongue, esophagus, heart, stomach and intestine. Nowhere was the mucous membrane involved. The lung and serous membranes were likewise unaffected. This condition gave the picture of pseudoscleroderma and macroglossia.

Three unusual cases of amyloid disease were recently reported from the Mayo Clinic by Bannick, Berkman and Beaver.[4] One case was associated with lymphosarcoma, another with gastric carcinoma

and in a third there was apparently no etiological factor of suppuration.

On the basis of the cases reported in the literature Lubarsch classified the atypical cases of amyloid into (1) amyloid with pseudoscleroderma, (2) amyloid with pseudomyotonia, and (3) amyloid with massive involvement of tongue, simulating neoplasm. There is no particular advantage in such an attempted classification.

In reporting a case of diffuse amyloidosis with deposition in unusual sites, Strauss [5] suggests the term "paramyloidosis" for this group of cases. He believes that in this type the amyloid is more frequently deposited in the musculature of the arterioles and small arteries of various organs and in mesenchymal tissue instead of in pericapillary and periglandular sites, as in typical amyloid disease. He collected 27 cases from the literature illustrative of unusual deposition of amyloid.

Case Reports

Case 1. B. H., a female, aged 53 years, was admitted with a history of dyspnea, cough and pain in the chest of several months duration, associated with loss in weight and increasing weakness. Six months prior to admission she had an attack of bronchopneumonia and an acute serofibrinous pleurisy. On admission the patient showed cyanosis of the lips and there was evidence of ascites. The heart sounds were distant and of poor quality, the rhythm regular and a systolic murmur was heard at the apex. The red blood cell count was 1,990,000, hemoglobin 40 per cent, white blood cells 10,400. The blood pressure was 104/80. The blood Wassermann test and the other laboratory findings were negative.

Two weeks after admission the patient developed a sudden attack of dyspnea, became cyanotic, her breathing became stertorous and she went into collapse and died on June 15, 1932.

The clinical diagnoses were congestive heart failure and (?) carcinoma or malignant tumor of the lung.

Postmortem Examination

The anatomical diagnoses were primary amyloid disease involving chiefly the heart, tongue, kidneys, lungs and gastro-intestinal tract; hypertrophy and dilatation of the heart; mural thrombi in right and left auricles; edema of the lower extremities; ascites; hydrothorax, bilateral; congestion, edema and partial atelectasis of the lungs; recent thrombosis of renal veins; arteriosclerosis of the kidneys.

The body was that of a well developed, poorly nourished, elderly white female in partial rigor. There was slight edema of the lower

extremities. A few hundred cc. of straw-colored fluid were present in the abdominal cavity. A little over a liter of clear straw-colored fluid was present in each pleural cavity. The lungs were partially collapsed. There were no adhesions.

Heart: The heart weighed 390 gm. The measurements were: pulmonic ring 7 cm., aortic ring 6.7 cm., mitral ring 9.2 cm., tricuspid ring 10.5 cm., left ventricular wall 12–13 mm., right ventricular wall 3–5 mm. The pericardium was normal. The heart had a peculiarly firm consistence. The left border was markedly rounded. On section the myocardium offered considerable resistance to cutting and presented a pale, grayish, waxy surface marked with translucent grayish streaks and with opaque yellow spots and streaks. A strongly positive test for amyloid was obtained with Lugol's solution.

In the left auricular appendage there was a soft mural thrombus with a smooth grayish surface and a soft reddish center. A few yellow, atheromatous patches were present in the aortic leaflet of the mitral valve. The left and right ventricles were considerably hypertrophied and slightly dilated. A few yellow, atheromatous patches were present in the sinuses of Valsalva. The valves were otherwise normal. Adherent to the pectinate muscles were three globular thrombi with a smooth gray surface and a soft reddish center, which ranged in size from 8 to 18 mm. The coronary arteries were smooth and widely patent.

Lungs: The lower lobe of the right lung was collapsed, noncrepitant, firm in consistence, dull reddish gray in color, and yielded a small quantity of clear fluid on pressure.

The left lung showed extensive atelectasis involving the entire lower lobe and the lower quarter of the upper lobe. Lugol's solution applied to the lung tissue apparently yielded a positive test for amyloid. The hilum and tracheobronchial lymph nodes were large and anthracotic.

Liver: The liver weighed 1050 gm. and measured 24 by 15.5 by 7 cm. The capsule was smooth. On section the surface was pale brownish and moderately congested. The test with Lugol's solution for amyloid was negative.

Spleen: The spleen weighed 110 gm. and measured 12.5 by 7 by 4 cm. The capsule was smooth, the organ firm, and on section the surface was purplish red. The markings were distinct. Amyloid test was faintly positive.

Kidneys: The right kidney weighed 105 gm. and measured 9.5 by 4.5 by 3 cm. The left weighed 110 gm. and measured 10.5 by 4.5 by 3 cm. The cortex measured 3–4 mm. and the medulla 15–18 mm. The kidneys were firm and decreased in size. The capsule stripped with ease, leaving a strikingly mottled, pale reddish yellow, coarsely granular surface with a number of larger shallow scars. On section the cortex was narrowed and uneven, pale yellowish and somewhat waxy in appearance. The markings were distorted. The cortex and the medulla were sharply differentiated. The test for amyloid was strongly positive. The renal veins, beginning about 1 to 2 cm. beyond the hilum of each kidney, were completely occluded by soft, friable, red and gray, partly lamellated thrombi, which involved also the ramifications in the kidney sinuses (Figs. 1 and 2).

Suprarenals: The right weighed 8.5 gm. and the left 9 gm. The cortex was bright yellow and the medulla somewhat autolyzed. The iodine test for amyloid was faintly positive.

A positive amyloid test was obtained in the bladder wall, vaginal wall, uterine wall and ovaries.

Lugol's solution yielded a dark brown color in the muscularis of the esophagus, stomach and intestines and dark brown spots in the mucosa of these organs.

Neck Organs: The tongue was definitely enlarged, due chiefly to a pronounced increase in thickness, and was unusually firm in consistence. On section it presented a strikingly pale yellowish brown surface with translucent grayish streaks. A strongly positive amyloid reaction was obtained. The mucosa of the epiglottis, larynx, trachea and main bronchi was pale. Lugol's solution applied to these structures yielded brownish spots (Fig. 3).

Bone: Sections of vertebrae and ribs presented no gross abnormalities.

Skeletal Muscle: Sections of diaphragm, psoas muscle and muscle of anterior abdominal wall gave a positive reaction for amyloid with Lugol's solution.

Microscopic Examination

Heart: Section of the *right auricle* shows most of the muscle replaced by a homogeneous pink-staining material. Among the trabeculations of the endocardium are thrombotic masses.

Section through *left ventricle* shows a diffuse infiltration of the myocardium with a peculiar homogeneous pink-staining material (amyloid). In these areas the musculature is atrophic. Muscle cells of the surrounding portions appear to be hypertrophic. In the areas of amyloid accumulation, muscle cells have undergone pressure necrosis. There is no cellular reaction, however, to the necrosis. In other sections of the heart amyloid material is present beneath both the endocardium and the pericardium (Fig. 4).

Lung: Marked atelectasis of the lung is seen. Many of the blood vessels contain peculiar homogeneous material in their walls which varies in amount in different parts of the lungs, but is particularly prominent in the small vessels. Amyloid material is present in the alveolar walls (confirmed by Congo red test).

Liver: Congestion of the central portions is present with vacuole degeneration of the nuclei of the cells. Some increase of the periportal connective tissue is seen. The walls of the arteries in the portal zones are thickened and strikingly infiltrated with amyloid (Congo red test). No amyloid is present in the parenchyma.

Spleen: The follicles are prominent and in many there is a peculiar homogeneous pink-staining material (amyloid). The vessels are somewhat thickened and amyloid is deposited in the walls of the arterioles (confirmed by Congo red test). The sinuses are markedly congested.

Tongue: There is extensive amyloid replacement of the muscle tissue. Striated muscle is everywhere atrophic and compressed by stringy, pink-staining, acellular material (Fig. 5).

Kidney: Extensive thickening of the capsule is present with numerous areas of scar tissue formation with extensive atrophy of tubular elements and glomeruli and round cell infiltration. Connective tissue about the scars has a pink-staining, homogeneous appearance. A few of the glomeruli are replaced by connective tissue arranged concentrically and some of these areas are hyalinized. Many of the tubules are distended with casts of albuminous material. Intervening blood vessels are congested and arterioles are everywhere markedly thickened and the lumens narrowed. Congo red test for amyloid is positive.

Colon and Stomach: Both show some replacement of the smooth muscle with acellular pink-staining material. Amyloid is also present in the submucosa. None is present in the wall of the gall-bladder.

Diaphragm: Shows striking atrophy of striated muscle and varying degrees of degeneration with pink-staining material present in the interstitial tissue.

Uterus: Amyloid is deposited in the walls of medium sized and small vessels and occasionally between the muscle fibers. In all instances the presence of amyloid in the tissues was confirmed by the Congo red test.

Comment

The unusual features of this case are the macroglossia due to amyloid infiltration of the tongue, the marked amyloid disease of the heart, lungs, colon, diaphragm and uterus, and the extensive dilatation and hypertrophy of the heart which eventually resulted in cardiac insufficiency and death. This resembles the case of Gerstel and Pick. In this case no infection of any kind was demonstrable. The cardiac hypertrophy was due probably to previous hypertension associated with renal arteriosclerosis. The presence of extensive amyloid disease in the myocardium is not responsible for the hypertrophy of the heart, in our opinion. Replacement of functioning cardiac musculature would not lead in itself to cardiac hypertrophy. Extensive fibrosis following coronary disease does not cause cardiac hypertrophy. No doubt, however, the extensive replacement of the heart muscle by amyloid contributed to myocardial insufficiency.

CASE 2. G. C., a female, aged 16 years, was admitted to the hospital May 4, 1930, complaining of pain in the joints of 10 years duration, associated with fatigue, general weakness, dyspnea at rest, and palpitation, and during the past 2 years progressive increase in size of the abdomen. Occasionally the joints were swollen and reddened. No fever was noted.

On examination the patient was found to be underdeveloped, poorly nourished and pale. A rachitic rosary with flaring of the costal margins of the ribs was present. The heart was somewhat enlarged and a blowing systolic murmur was heard at the apex. Blood pressure was 124/80. The abdomen was large and the superficial abdominal veins were prominent. The liver edge could be felt 10 cm. below the costal margin, the spleen 4 cm. below the costal margin. There was some limitation of motion of the right elbow and left wrist. The axillary, submaxillary and inguinal lymph nodes were enlarged.

At the time the patient was admitted the red blood cell count was 2,500,000, hemoglobin 47 per cent, white blood cell count 7500. The Van den Bergh reaction was delayed and slightly positive (0.4 mg. per cent). The Congo red test showed a retention of 88 per cent of the dye after 1 hour. The blood urea nitrogen was 69.2 mg. per 100 cc., creatinine 2 mg. per 100 cc. A marked decrease in the urea concentrating power was found. The renal concentration showed a

specific gravity of 1.008–1.010. The urine contained a large amount of albumin and was loaded with hyaline and granular casts. The phenolsulphonephthalein test showed a 10 per cent output of the dye in 2 hours. The blood serum calcium was 8.9 mg. per cent, the blood serum phosphorus 8.3 mg. per cent. Successive determinations showed increases in urea nitrogen and creatinine concentration. A diagnosis of chronic glomerulonephritis with renal insufficiency and uremia was made.

During her stay in the hospital the patient had several attacks of arthritis with involvement of the ankles. Ten months after admission she had sudden epistaxis, vomited blood and became hyperpnoeic. A tachycardia was noted, and purpuric spots appeared on the arms. The fundi showed slight swelling of the discs. The urea nitrogen was 108.6 mg. per 100 cc., the creatinine 7.3 mg. per 100 cc. and the CO_2 combining power 17.6 volumes per cent. The CO_2 combining power several days later was 54 volumes per cent, the urea nitrogen rose to 154.1 mg. per 100 cc. with a creatinine of 10.5 mg. per 100 cc.

The spinal fluid was under slightly increased pressure. Several days later the patient had a convulsion and on examination a bilateral inexhaustible clonus was elicited. During the same period an acute purulent parotiditis developed. Following incision and drainage the parotiditis cleared up and the patient improved. Apathy continued with occasional attacks of fever. From December 1931 until April 1932 three transfusions were given. Purpuric spots were again noted in July 1932. Attacks of paroxysmal dyspnea associated with gallop rhythm and wheezing râles in the chest occurred during August. Late in August, 2 years and 4 months after her first admission, she developed signs of myocardial insufficiency with enlargement of the liver and pulmonary congestion. The blood pressure rose to 180/94. The patient was orthopneic and her condition became progressively worse, pallor increased and gallop rhythm persisted. A precordial friction rub was heard over the sternum and on Aug. 29, 1932, the patient became markedly dyspneic and died.

The clinical diagnoses were chronic glomerulonephritis with progressive renal insufficiency and uremia; myocardial insufficiency, gallop rhythm and congestive heart failure; ankylosis of right elbow, partial in left wrist, and recurrent acute arthritis.

Postmortem Examination

The anatomical diagnoses were amyloidosis of kidneys with contraction; amyloidosis of suprarenals and liver; hypertrophy and dilatation of heart; fibrinous pericarditis; chronic passive congestion of lungs, liver, spleen and gastro-intestinal tract; juvenile rickets (clinical); ankylosis of right elbow joint; infantile genital tract.

The body was that of a poorly developed and poorly nourished white female, 142 cm. in length, in complete relaxation. Pelvic and axillary hair was totally absent. The breasts were small. There was marked pallor of the skin and mucous membranes with a subicteric tint. The face was puffy and the neck veins prominently distended. There were scattered purplish blue blotches on the skin of the an-

terior neck and upper extremities. About 150 cc. of serosanguineous fluid were present in either pleural cavity. There were few adhesions.

Heart: The heart weighed 350 gm. The measurements were: pulmonic ring 6.5 cm., aortic ring 6 cm., mitral ring 9 cm., tricuspid ring 9.5 cm.; right ventricle measured 6 mm., left ventricle 18 mm. The pericardial sac contained no fluid. A thin fibrinous deposit was present over the midportion of the anterior wall of the left ventricle and adjacent right ventricle. There were moderate dilatation and hypertrophy of right and left auricles and right ventricle. There was marked hypertrophy with dilatation of left ventricle. Valves and coronary arteries were normal. The myocardium had a dull, light red color.

Liver: The liver weighed 1320 gm. and measured 24 by 18 by 7 cm. The capsule was smooth and the parenchyma a diffuse dull brown with an icteric tint.

Spleen: The spleen weighed 380 gm. and measured 16 by 11 by 5 cm. The organ was enlarged, firm and rubbery in consistence. The capsule was smooth. On section the parenchyma was deeply congested and the markings indistinct. The pulp did not scrape away. Iodine test for amyloid was negative.

Kidneys: Each kidney weighed 50 gm. and measured 8.5 by 5 by 2.5 cm. The cortex measured 2 to 3 mm. and the medulla 12 to 14 mm. The organs showed an identical and striking picture, being markedly contracted and firm. The capsule stripped with slight difficulty, leaving a light, yellowish red surface dotted with many minute, pin-point, glassy and grayish, slightly raised elevations between which were innumerable pin-point to pin-head-sized yellowish dots and streaks. The organs cut with increased resistance. In some places the cortex was narrowed, measuring 2 to 3 mm., and was not sharply delimited from the medulla. Cortical and medullary architecture was replaced by numerous fine and coarse, irregular, light yellowish streaks. The parenchyma had a waxy appearance and gave a strongly positive iodine test. There were a few petechiae in the pelvic mucosa.

Suprarenals: The right suprarenal weighed 10 gm., the left 9 gm. The organs were enlarged and firm. There were several adenomatous cortical nodules of similar appearance, the largest measuring 0.5 cm. in diameter and about 3 mm. in width. The cortex was dull gray and waxy in appearance. The medulla appeared normal. Amyloid reac-

tion was positive in the cortex. There was no evidence of amyloid in the gastro-intestinal tract, including the tongue.

Elbow Joint: The right elbow joint was ankylosed in a position of 170° extension, due to thickening and shortening of the capsule. Numerous thin, easily torn, fibrous adhesions extended between the borders of the articular surface of the humerus and ulna. The cartilaginous articular surfaces were slightly rough, but there were no adhesions between them.

Microscopic Examination

Heart: Hypertrophy of fibers and nuclei, with marked cloudy swelling and fragmentation is present. There is moderate increase of interstitial tissue with foci of lymphocytic infiltration. Epicardial fat is increased and contains many scattered lymphocytes, plasma cells and monocytes. The intima of the main coronary artery shows slight subendothelial swelling, lipoid infiltration with degeneration and hyalinization.

Liver: Marked parenchymatous degeneration and congestion is seen. There are areas in which the entire lobule, except for a narrow zone at the periphery, is completely destroyed and replaced by pink-staining, fibrillar substance in which there are occasional mononuclear cells with hemosiderin, scattered erythrocytes and ghosts of preëxisting hepatic cells. At the periphery there are a few red blood cells in the parenchyma suggesting recent hemorrhage. There is slight increase of periportal connective tissue with lymphocytic infiltration. The arterioles are thickened.

Spleen: The sinuses are markedly dilated and congested and the pulp is atrophic. Malpighian corpuscles are fairly prominent.

Kidney: The glomeruli are closely crowded, large and replaced, except for a few scattered nuclear elements, by amyloid. The glomerular tufts are fused with the capsule which is also thickened by amyloid. There is a marked diffuse increase of interstitial tissue. The great majority of the tubules are markedly atrophic. However, there are areas in which the tubules are widely and irregularly dilated, evidently compensatory. There are frequent, small, focal collections of lymphocytes and plasma cells in the interstitial tissue. The arterioles show considerable thickening with amyloid and narrowing or obliteration of the lumens. The interlobular and arcuate

arteries show fairly marked medial hypertrophy with subendothelial deposition of a lipoid substance. Other arteries of the same size show complete obliteration of the normal architecture with a fibrillar acellular tissue, probably hyalinized connective tissue (Fig. 6). In some areas there are calcific deposits in the medulla, which seem to have replaced tubular epithelium.

Suprarenal: Sections show almost complete replacement of cortex and medulla by amyloid material. There are occasional small islands in the zona glomerulosa and in the medulla which are spared, but these show extensive degeneration. Within the cortex there are occasional calcific plaques.

Pituitary: The anterior portion contains a few, small, irregular cysts filled with amorphous, pink-staining material and lined by a single flat layer of basophilic or eosinophilic cells. There seems to be a slight increase of basophilic cells.

Comment

This case presents several unusual features. The only infection was chronic arthritis, which was not suppurative, with ankylosis of one joint. At the time the complicating parotiditis occurred, evidence of uremic symptoms were manifest. Amyloidosis in a child of 16 years is in itself rare. Amyloid was deposited in the kidneys, suprarenals and liver. The severity of the amyloid deposition in the kidney led to marked renal insufficiency and hypertension, and the patient died of uremia. Uremia, complicating amyloidosis of the kidney, has been observed not infrequently, but it is beyond the scope of this paper to review this problem.

CASE 3. S. S., female, aged 63 years, admitted April 13, 1933, complaining of progressive asthenia, constipation and anorexia, and loss of 50 pounds in weight during the preceding 2 years. During this period she had frequent attacks of diarrhea with watery and bloody stools accompanied by rectal tenesmus. For some time prior to admission she complained of severe headaches and a year before admission to the hospital had suffered a temporary loss of memory associated with mental confusion and disorientation, which at the time was attributed to a cerebral insult. For 6 months she had complained of epigastric pain. At another institution signs of congestive heart failure, pulmonary edema, right hydrothorax and a gallop rhythm had been found. The electrocardiogram showed a cove plane T_1. The blood urea was 30 mg.

On admission to the hospital there was slight cyanosis of the lips, moderate dyspnea and the carotid arteries were markedly sclerotic and tortuous. The heart was enlarged to the left. A systolic apical murmur was heard at the apex

and gallop rhythm was present; the apical primary sound was reduplicated. The superficial peripheral vessels were sclerotic. The epigastrium was tender and the liver edge was felt three fingers below the costal margin. A midline low abdominal scar was present. The blood pressure was 122/86. The fundi showed narrow shiny vessels, degenerative changes in the macula attributed to anemia.

On fluoroscopy the heart was horizontal, the left ventricle moderately enlarged; the other chambers were thought not to be enlarged. The ascending limb of the aorta was elongated, the supraventricular portion dilated, the entire descending limb being greatly dilated with a circumscribed bulge in its middle third. The aorta gave a picture suggestive of localized aortic aneurysm. Small pleural effusions were found at both bases.

Thoracentesis had to be repeatedly performed, with removal of from 700 to 1000 cc. of fluid from each side.

On June 17, 1933, 2 months after admission the patient complained of substernal oppression and dyspnea. The liver edge was felt two fingers below the costal margin. The fluid reaccumulated so that thoracentesis had to be repeated.

Progressive azotemia appeared and vomiting continued. The urea nitrogen, which was 34.6 mg. per 100 cc. on admission, rose to 101.6 with a creatinine concentration of 10 mg. per 100 cc.; blood proteins were reduced, the serum albumin, being 2.76 mg. per cent, globulin 1.90 mg. per cent, the blood serum calcium 7.9 mg. per cent, phosphorus 8.7 mg. per cent, and the blood CO_2 35 cc. per 100 cc.

Generalized anasarca became more marked and on July 27, 1933, the patient developed a marked tachycardia, which by electrocardiogram proved to be auricular flutter with a 2:1 block. The same day an impure flutter with fibrillation appeared. On 22 cat units of digitalis regular rhythm was restored within 48 hours.

Despite treatment edema persisted and simultaneously the total blood proteins were further reduced to a serum albumin of 2.53 mg. per cent and a globulin of 1.46 mg. per cent. The blood urea rose to 109.2 and the creatine to 11.3 mg. per cent.

On Sept. 4, 1933, she had a generalized convulsion and following the convulsive seizure was comatose, had a tachycardia, and the blood pressure fell to 82/55. A few minutes later, however, she came out of the coma, was incontinent of urine, became very weak, vomited and died suddenly on Sept. 5, 1933.

The clinical diagnoses were (?) carcinoma of the gastro-intestinal tract, coronary artery disease and vascular renal disease with uremia.

Postmortem Examination

The anatomical diagnoses were amyloid contracted kidneys; thrombosis of renal veins (bilateral); generalized arteriosclerosis; aneurysm of descending aorta (arteriosclerotic); atherosclerosis of coronary arteries with occlusion of left anterior descending branch; healed myocardial infarction of left ventricle and interventricular septum; mural thrombus of left ventricle; chronic passive congestion of liver and spleen; adenomas of thyroid; ulcers of duodenum, and bilateral hydrothorax.

The body was that of a poorly nourished and poorly developed,

elderly white female about 155 cm. in length, moderately emaciated and in semirigor with moderate edema of arms, lower extremities and back, and with slight cyanosis of lips and finger tips. There were some moderately firm adhesions of omentum to the parietal peritoneum of the anterior abdominal wall. About 100 cc. of clear yellow fluid were present in the pelvis. The uterus was retroverted, and the tubes were matted in a mass of adhesions to the rectal wall of the cul de sac. The diaphragm was at the level of the fourth space on the right and at the fifth space on the left. Each pleural cavity contained about 1500 cc. of clear, amber-colored serous fluid.

Heart: The measurements were: pulmonic ring 7.5 cm., aortic ring 7 cm., mitral ring 8.5 cm., tricuspid ring 11 cm., left ventricular wall 17 mm., right ventricular wall 1 to 2 mm. There were no adhesions. The right border was made up entirely of right auricle. There was a marked increase in amount of epicardial fat over the right side of the heart. The organ was soft and flabby. The apical region of the left ventricle and lateral surface adjacent to it sank in so that a depressed area 3 cm. in diameter was visible on this lateral aspect of the left ventricle. The myocardium was grayish red with many fine gray streaks throughout. There was marked thinning of the myocardium in the lower half of the interventricular septum and in the lateral aspect of the left ventricle and the apical region corresponding to the depressed area on the surface. Adherent to the lower half of the interventricular septum in the left ventricle was a firm, grayish pink, oval mass about 3.5 by 2.5 cm. protruding slightly into the ventricular cavity. It cut with ease and in the depths adjacent to the thinned-out muscle it was broken-down and yellow. At the junction between the adherent clot and the thinned myocardium was a fine layer of firm, yellow, apparently calcified material. The endocardium of the entire left ventricle was markedly thickened, white and opaque. Gray streaks were visible through the endocardium of the right ventricle over the region of the interventricular septum. There was no hypertrophy or dilatation of any of the chambers. The valve leaflets of the tricuspid, aortic and pulmonic valves were normal. The aortic leaflet of the mitral valve was thickened by a raised, yellow, atherosclerotic plaque. There was slight thickening at the base of the mitral valve leaflets.

The coronary arteries were thickened and tortuous. There were raised, calcific, atherosclerotic plaques in their walls. The anterior

descending branch of the left coronary was markedly narrowed in its proximal third and in one area completely occluded by a yellowish calcific mass which contained a fine recanalized lumen.

Lungs: Both were rather small, having been compressed by fluid. They were crepitant throughout, mottled grayish black and cut with ease. The cut surface was reddish gray. In several small branches of the pulmonary artery there were adherent, grayish yellow, firm clots.

Liver: The liver weighed 800 gm. and measured 19 by 17 by 7 cm. The organ appeared smaller than normal, was firm and of a light brown color. The capsule was smooth and cut with normal resistance, revealing well defined hepatic markings with alternating brown and yellow streaking. Amyloid test with iodine was negative.

Spleen: The spleen weighed 100 gm. and measured 9 by 7 by 3 cm. The organ was small, firm and rubbery and cut with increased resistance, revealing a reddish purple cut surface with distinct markings. The pulp did not scrape away. The amyloid test was negative.

Kidneys: Each weighed 100 gm. and measured 8 by 3.5 by 2 cm. The cortex measured 3 mm., the medulla 11 mm. The organs were small and firm, and the capsule stripped easily, revealing a finely granular, grayish pink and yellow surface. They cut with resistance, the cut surface showing a ground-glass, yellowish pink appearance. The markings were poorly defined, the cortex was narrow and poorly differentiated from the medulla. The small vessels gaped slightly. Arcuate veins were occluded by grayish pink, firm clots. There was a strongly positive amyloid test with iodine. The pelves and ureters were normal. Both renal veins were occluded by grayish pink, moderately firm material. Occluding tissue extended into the veins of the parenchyma but did not extend out to the junction of the renal vein with vena cava.

Pelvic Organs: The tubes were adherent to the posterior wall of the cul de sac. The ovaries could not be definitely located but they may have been incorporated in the adhesions. Uterus and bladder were normal.

Thyroid: Of normal size and shape, weighing 22 mg. At the lower pole of the right lobe was a hard mass 2.5 cm. in diameter, apparently encapsulated, which on cut section was yellow and quite firm. The thyroid tissue was pink and contained numerous small, grayish pink nodules, which were softer than the surrounding parenchyma. A

few of these contained grayish fluid. Others were solid, and a few were stony hard.

Blood Vessels: The entire aorta was inelastic and was the seat of marked atherosclerotic changes. The ascending portion was dilated from above its origin to the arch, forming a slight pouch. In this region the aorta was elastic and contained relatively few raised yellow flecks. The arch and openings of the cephalobrachial vessels showed more numerous raised areas, a number of which were firm and hard. The descending aorta from the arch into the vessels of the lower extremities was markedly thickened and there was very little normal intima visible. The intima was replaced by yellowish hard plaques and shallow, irregular ulcerated areas covered with clot and irregular, hard, shell-like flattened tissue. At the region of bifurcation calcification and ulceration were most marked. In the midportion of the descending thoracic aorta was a knob-like protrusion to the left, about 4.5 by 3 cm. This pouching of the aorta was made up of the outer coats of the artery and was filled with an old, lamellated, partly organized thrombotic mass. The large branches of the aorta were all thickened and tortuous, especially the renal and splenic arteries which were bony hard. The splenic artery turned upon itself so that it formed a "snail shell" structure. The mesenteric arteries showed very slight atherosclerotic thickening but no occlusion. The inferior vena cava was normal. There was moderate atherosclerotic thickening of the smaller pulmonary vessels and a few grayish clots in the small arteries.

Pituitary: The organ was much smaller than normal.

Brain: Grossly normal. In the left occipital cortex there was a small area suggesting a mild scarring. All the vessels showed marked arteriosclerotic changes.

Amyloid was demonstrable in the kidneys, liver and spleen.

Microscopic Examination

Liver: Fatty change is seen in the liver cells, particularly in the periportal region. Slight congestion of central veins is present. Walls of arteries contain amyloid, as detected by Congo red stain.

Spleen: The follicles are not prominent. Arterioles of malpighian bodies are markedly thickened, the lumens narrowed. There is hyalinization of the walls of many of the vessels. The pulp shows a considerable degree of congestion and marked increase in

connective tissue. The malpighian arterioles contain amyloid and scattered throughout are streaks of amyloid.

Suprarenal: A considerable amount of lipoid accumulation in fascicular and glomerular layers is present. There is a large quantity of amyloid in the cortex, which in places extends beneath the endothelium of the capillaries and is accumulated in large quantities, obliterating the cellular structure of the parenchyma.

Heart: Extensive scar tissue formation in the myocardium with replacement fibrosis of muscle is present. Hypertrophy of muscle fibers is moderate. Section through the left ventricle in the region of the lamellated thrombus shows extensive fibrosis of myocardium, vacuolization of muscle fibers with hypertrophy of remaining cells. Marked fibrous thickening of endocardium is seen. Overlying the endocardium, and partly attached to it, is a pink-staining material containing large calcific plaques. Some degree of organization is present at the base of the thrombotic mass.

Kidney: The glomeruli are entirely replaced by a pink-staining, acellular, amorphous material. Ghosts of glomeruli are seen. Many of the glomeruli are small, irregular or completely destroyed with not a single intact glomerulus in the sections. There is a marked increase in interstitial connective tissue with a varying degree of atrophy of involved tubules. In some areas the tubules are dilated and filled with pink-staining material. In other areas they are reduced to a fine lumen and flattened epithelium. There are areas of round cell infiltration in the interstitial tissue. The arterioles are thickened, the lumens reduced in size, and the walls are replaced with a homogeneous material, which stains deeply with Congo red. Amyloid is found also in the medulla beneath the epithelium of the tubules.

Aorta: There is marked thickening of the intima with replacement fibrosis of connective tissue which is extensively hyalinized. The intima shows numerous cholesterin crystal spaces and areas of calcification which extend into the media.

Comment

Several interesting features are present in this case. The history was unusual in that the progressive loss of weight, asthenia, anorexia and abdominal pain suggested an intra-abdominal neoplasm. The X-ray of the chest was further misleading in that a localized arteriosclerotic aneurysm in the descending aorta simulated a primary

malignant growth. The hydrothorax requiring repeated thoracentesis, the gallop rhythm, the edema of the dependent parts and the hepatic enlargement fit into a picture of congestive heart failure associated with extensive myocardial infarction and are probably unrelated to the amyloid disease. It is noteworthy that the amyloid disease, as in Case 2, was practically limited to the kidneys and was sufficiently severe to cause uremia and a marked reduction of blood proteins simulating a picture of a nephrosis. There is no apparent etiological factor present, indicated either by the history or by the autopsy findings, for the amyloid disease.

Discussion

The frequent association of the deposition of amyloid material in the various organs with chronic suppurative processes led to the conception that this metabolic disturbance is dependent on continued destruction of tissue protein. The nature of amyloid material was investigated by many workers.[6] The protein nature of amyloid was pointed out by Friedreich and Kekulé [7] in 1859 and substantiated by Kühne and Rudneff [8] in 1865. It was found that amyloid organs contain chondroitin-sulphuric acid. On the basis of this observation Krawkow [9] devised a method for the extraction of amyloid and found it to be a compound of protein with chondroitin-sulphuric acid. This view was contradicted by the work of Hanssen,[10] who studied amyloid isolated mechanically from sago spleens in pure form, and found that this material contained no chondroitin-sulphuric acid, although the amyloid organs contained an excess of sulphur as sulphate. Eppinger [11] analyzed chemically the amyloid obtained from a solitary amyloid mass in the liver. He found that the dried material yielded no phosphorus and no sulphur but contained purines, diamino acids, much tyrosine and no carbohydrate. Of the amino acids present, glycocoll and phenylalanine, tyrosine, leucine and alanine comprised 42 per cent, arginine 14.67 per cent, tryptophane 4.41 per cent, glutamic acid and asparaginic acid 13.08 per cent. No cystine or histidine was present.

Experimentally it has been shown that the injection of bacteria such as staphylococci and various culture filtrates, and chemical agents such as sodium caseinate, may produce extensive amyloid disease in the spleen, liver or other organs of mice. Even the injection of turpentine with the production of a sterile abscess may call forth an amyloid reaction.

Kuczynski,[12] who succeeded in producing amyloid disease in mice by the injection of 5 per cent sodium caseinate solution, also found it could be produced by the feeding of proteins. These findings were confirmed by many investigators.

Letterer [13] observed amyloid deposition in mice by the injection of egg-white, gelatin, nuclein, zein, peptone, casein-peptone and Witte's peptone. He concluded that many parenterally injected proteins may give rise to amyloid. He further found that amyloid disease could be produced in a few days by implantation of a piece of sterile mouse spleen or liver into the peritoneum.

The ease of production of amyloid disease in mice and the frequent spontaneous occurrence in this animal, as mentioned by Wells,[14] cast some doubt on the validity of the conclusions drawn from such experimental studies.

Considerable controversy has arisen concerning the reversibility of amyloid disease. In view of the cases reported, both in this and in other communications of amyloid unassociated with apparent suppuration, this question is of considerable importance. Leupold [6] demonstrated that amyloid deposition may be a reversible process. Kuczynski [12] believed that amyloid may be digested by the endothelial cells of the liver. He found these cells in mice filled with amyloid after the injections of the caseinate used to produce this process had been discontinued. Morgenstern [15] confirmed this observation in amyloidosis produced by parenteral injections of albumin. He produced typical amyloidosis in 25 to 50 days in white mice. In other studies Morgenstern [15] gave nutrose to white mice for 30 to 40 days and confirmed the presence of amyloid in the liver by biopsy. Biopsies were again taken 2 weeks after the injections were discontinued. After many months the animals were killed. The amyloid showed marked regression after 2 months. The deposits were surrounded by a granulomatous tissue containing fibroblasts, occasional giant cells and newly formed capillaries. Much less amyloid was apparent after 3 months. Four months after the injections had been discontinued complete resorption and disappearance of the amyloid occurred in some cases. He concluded that if the cause of the amyloid disappears, the amyloid deposits will disappear also.

Dantchakow [16] also observed the absorption of amyloid in mice 2 months after discontinuing the injection of staphylococci. She

noted, however, that if the amyloid deposits were considerable, they were still present 6 months after the injections were discontinued, and she believed that amyloid was not resorbed if present in large amount.

It is conceivable that in the cases reported in this communication in which no apparent source of suppuration had been found that some previous suppurative process initiated the disturbance in protein metabolism. This, however, would seem unlikely. There have now been reported in the literature at least 6 other cases of diffuse amyloidosis in the absence of any suppurative process. It would seem likely that under certain conditions a fundamental disturbance in protein metabolism may occur which results in this abnormal deposition of an unusual protein. It would be interesting to investigate whether the diet plays any rôle in such a disturbance in human beings.

Summary and Conclusions

Three unusual cases of amyloid disease are reported in which an etiological factor was not demonstrated. The first was a female, 53 years of age, with extensive amyloid disease of the heart, tongue, gastro-intestinal tract and other organs, who died of congestive heart failure. The second case was a female, 16 years of age, with extensive amyloid deposits in the kidneys, liver and suprarenals, who died of uremia. She had an ankylosis of one joint without any evidence of suppuration. The third case was a female, 63 years of age, with amyloid contracted kidneys, who eventually died in uremia. She had a severe coronary sclerosis with an old occlusion of the descending branch of the left coronary artery and a healed infarction of the left ventricle. The amyloid disease was limited to the kidneys.

In view of the absence of any apparent suppuration it is suggested that this peculiar disturbance in protein metabolism may be independent of tissue destruction.

Addenda: After this article had been completed, Budd reported a case of primary amyloid disease of the heart in the *American Journal of Pathology*, 1934, **10**, 299. In this case there was an extensive carcinoma of the prostate with extension into the bladder and surrounding tissues, a pyonephrosis and an acute endocarditis.

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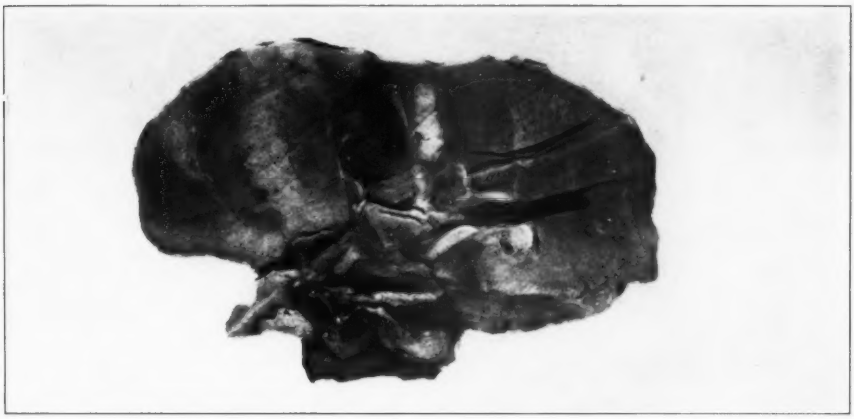
DESCRIPTION OF PLATES

PLATE 10

FIG. 1. Case 1. Kidney. Cut surface showing narrow indistinct cortex and waxy appearance.

FIG. 2. Case 1. External surface of kidney showing contraction and coarsely granular surface.

FIG. 3. Case 1. Tongue, showing macroglossia.



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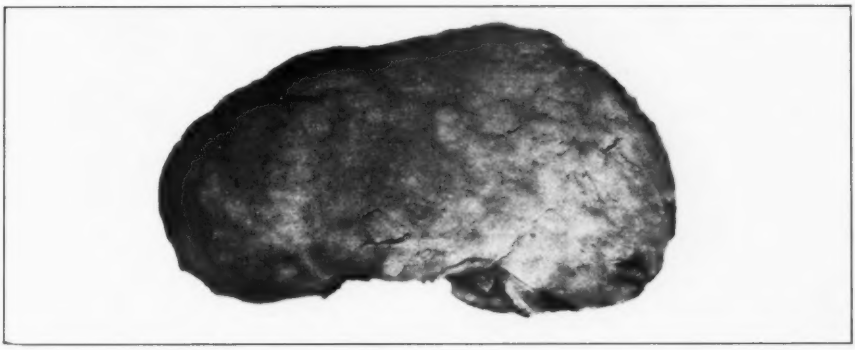

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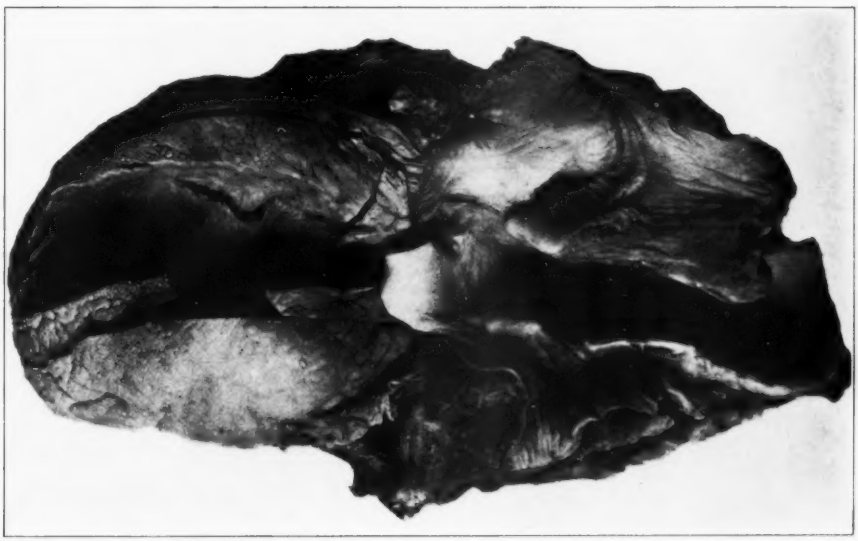

3

PLATE II

FIG. 4. Case 1. Microscopic section of the heart showing amyloid infiltration. × 240.

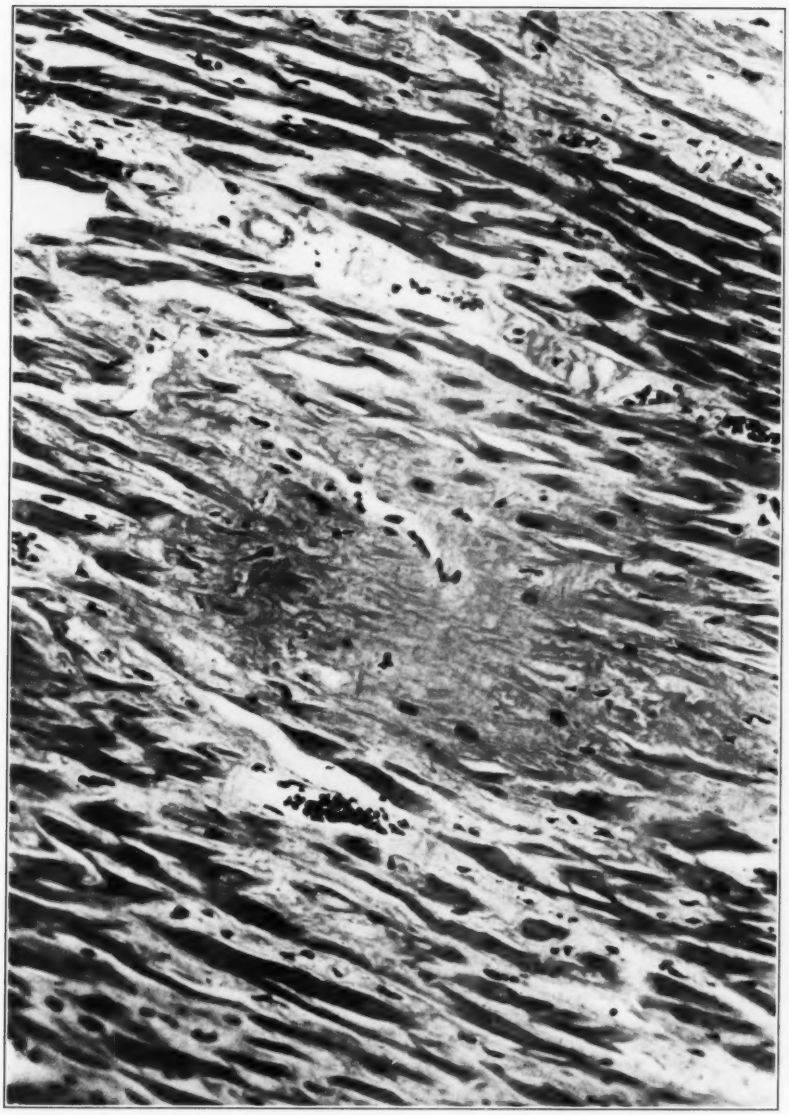

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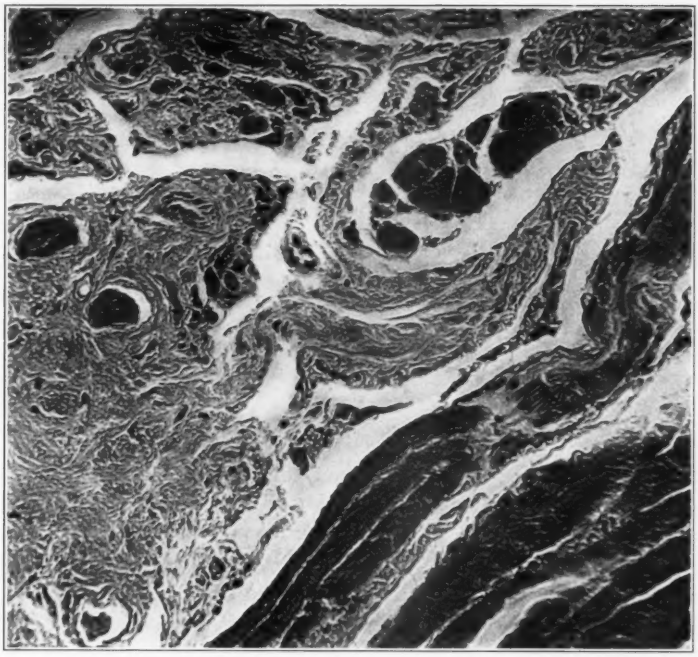
PLATE 12

FIG. 5. Case 1. Microscopic section of the tongue showing amyloid infiltration of the muscle. × 240.

FIG. 6. Case 2. Microscopic section of the kidney showing severe amyloid infiltration. × 240.



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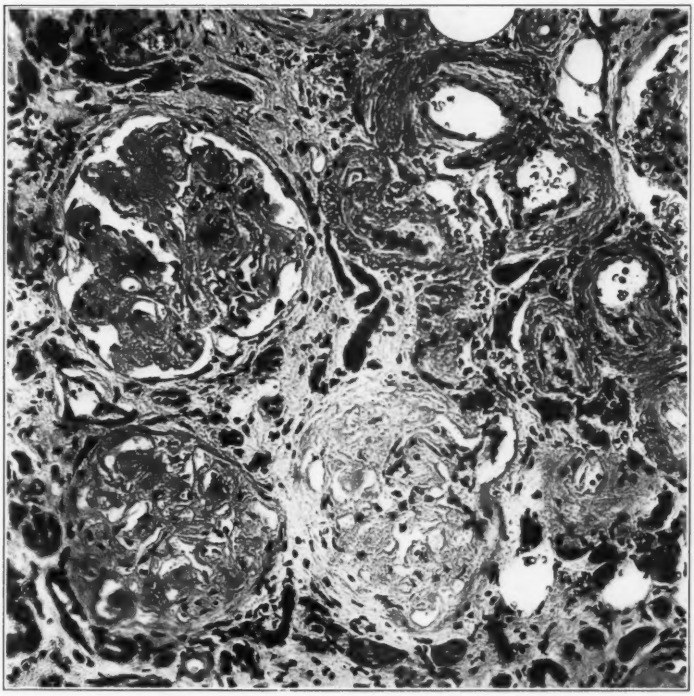

6

SUBACUTE LYMPHATIC LEUKEMIA *

HISTOGENETIC STUDY OF A CASE WITH THREE BIOPSIES

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The problem of the histogenesis of lymphatic leukemia still has many unsettled points. Therefore, it seemed of interest to follow the development of a case of lymphatic leukemia from the earliest stage. The pathologist usually has the opportunity to examine only material from advanced stages showing the pathological changes at the moment of death. We had the opportunity to observe a case of subacute lymphatic leukemia and to obtain biopsied inguinal lymph nodes at three different periods during the progress of the disease. These nodes show different stages in the development of the histopathology that is so characteristic of the postmortem material. They also explain important changes in the blood picture which occurred during the progress of the disease.

The hematopoietic activity of the reticulum was repeatedly emphasized by Maximow,[1] Downey and Weidenreich,[2] Klemperer,[3] and others, and recent literature gives increasing data regarding the participation of the reticulum in the leukemic process. The best evidence for this is in the so-called leukemic reticulo-endotheliosis, or monocytic leukemia of the Schilling type. Fineman,[4] Tice and Jaffé,[5] and others also claim that this occurs in other types of leukemia. However, the postmortem material rarely shows any evidence to support this claim. Fineman's [4] observations were made on biopsy material and he obtained good evidence for the derivation of the immature lymphocytes from the reticulum in a case of subacute lymphatic leukemia. The three biopsies and the postmortem material of the case which is reported here seemed to furnish ideal material for the further study of this question.

* Received for publication July 16, 1934.

Report of Case *

Clinical History: The patient was a white male, 6 years of age. The history obtained from the parents on admission was as follows. Chief complaints were pallor, weakness, epistaxis, and generalized lymphadenopathy of 6 months duration. In July, 1933, bleeding from the left nostril occurred, continuing for 3 days. He was studied in another hospital a few weeks prior to admission and the diagnosis of lymphatic leukemia was made. Three deep X-ray treatments were given, the white cell count varying in the meanwhile from 40,000 to 21,000. Three days prior to admission to the University Hospital epistaxis began again and the patient was admitted in an extremely dehydrated condition.

Physical examination revealed a very anemic boy with marked dyspnea. Both ears showed a profuse, purulent discharge. The neck showed bilateral cervical adenopathy. The chest organs were without abnormalities. The spleen was markedly enlarged, extending below the costal margin. The liver was not felt.

Blood Examination: On admission the hemoglobin was less than 10 per cent, red blood cells 800,000, white blood cells 10,000. The blood smear disclosed a marked anisocytosis, poikilocytosis and hypochromasia. The neutrophil leukocytes showed marked toxic changes. There were occasional immature lymphocytes and large reticulo-endothelial cells.

The patient received seven blood transfusions within the next 14 days and responded with a marked improvement, the hemoglobin rising to 51 per cent.

Because the blood examinations revealed many large reticulo-endothelial cells in addition to the mature and immature lymphocytes, a right inguinal lymph node was removed on Jan. 6, 1934, for the purpose of clearing up the diagnosis. The lymph node was enlarged. The imprint preparation of the node showed the presence of immature lymphocytes, and sections revealed a marked hyperplasia of the reticulum.

During the following 2 months the patient was able to be up and around and seemed to be experiencing a remission. The white cell count ranged around 35,000, with 96 per cent lymphocytes, the majority of which were of the immature type. The blood picture therefore indicated a diagnosis of lymphatic leukemia, while the lymph node of the first biopsy material revealed only a marked hyperplasia of the reticulum.

On Feb. 7, 1934, a second biopsy of a left inguinal lymph node was performed. A markedly enlarged node measuring 2 by 1.5 by 1 cm., hard, with a pinkish gray transparent cut surface was removed and examined. Feb. 27, 1934, a third biopsy was performed, with essentially the same findings. A few weeks later the patient became very weak, the temperature rising to 105°. He also developed eruptions over the entire body. Additional blood transfusions were given without results and the patient died quite suddenly March 8, 1934.

Postmortem Examination

The report of the findings is restricted to the pathological changes. Autopsy was performed 15 minutes after death.

* For the case report and the use of material we are greatly indebted to Professor I. McQuarrie, Head of the Department of Pediatrics, University Hospital.

The body is that of a poorly developed, undernourished white male, 6 years of age. The skin is markedly anemic. Multiple petechiae are present on the trunk, but are most numerous on the back. There is a slight discharge in the left ear. The liver is markedly enlarged, reaching almost to the iliac crest. The heart is slightly enlarged. The muscles of both ventricles are flabby. Multiple small nodules are scattered in the lungs. The spleen weighs 440 gm., is quite hard and shows indistinct follicles. The liver weighs 1425 gm., is hard, and on the brownish red cut surface numerous pin-head-sized yellowish areas are seen. Generalized lymphoadenopathy is present. Both kidneys are pale and flabby with numerous petechiae.

Anatomical Diagnoses: Edema of lungs, subacute lymphatic leukemia, bilateral otitis media suppurativa.

Microscopic Examination

The liver presents massive subcapsulary and portobiliary infiltration of mononuclear cells with basophilic cytoplasm. The sinusoids are relatively free of the infiltration. In the spleen the malpighian bodies are markedly enlarged; some areas are normal, but most of the organ shows complete obliteration of the structure with an overgrowth of cells. The lymph nodes in the mesenteric region present uniformly dense masses and branching cords of cells. The kidneys are extensively infiltrated. The lungs show marked edema. There is a small area of peribronchial infiltration.

Study of the Blood

Blood examination on admission showed hemoglobin less than 10 per cent, red blood cells 800,000, white blood cells 10,000. The differential count was eosinophils 0 per cent, basophils 0 per cent, band forms 0 per cent, segmented cells 35 per cent, lymphocytes 58 per cent, monocytes 0 per cent, reticulo-endothelial cells 7 per cent. Marked anisocytosis, poikilocytosis and hypochromasia were present. The segmented leukocytes showed marked toxic changes. Daily examination of the blood revealed the presence of large reticulo-endothelial cells and some immature lymphocytes. These large reticulo-endothelial cells in smears stained with May-Grünwald-Giemsa were characterized by abundant, pale bluish cytoplasm containing some yellowish hyaloplasm in very small vacuoles, and a

relatively small nucleus with a fine and regular chromatin network and distinct parachromatin, with more or less indistinct nucleolus. In many instances the leptochromatic nuclear pattern of these large cells had become coarser, so that the nucleus resembled the nucleus of a lymphocyte, while the cytoplasm was still of reticulo-endothelial type (Figs. 1, 2 and 3). Cells having a distinct lymphocytic nucleus, but with cytoplasm of reticulo-endothelial type like the cell shown in Figure 4, were also found.

Sixty to 85 per cent of the lymphocytes were of immature type. These immature lymphocytes, when stained with May-Grünwald-Giemsa (Pappenheim), were characterized by a large nucleus and a small amount of definitely basophilic bluish cytoplasm. The nucleus presented an extremely fine and regular chromatin network and an abundant and distinct parachromatin, which was composed of numerous, fine, minute rounded granules embedded in a continuous mass of chromatin (leptochromatic structure, as shown in Fig. 5). These immature cells often possessed definite nucleoli. The immaturity in many instances was so marked that it was not possible to tell the direction of the differentiation. Occasionally the presence of immature cells with very fine nuclear pattern, having one or two distinct nucleoli and definitely basophilic cytoplasm (lymphoidocyte of Pappenheim, myeloblast of Nägeli) was noted. Similar cells having azure granules in the bluish cytoplasm and possessing a leptochromatic nuclear pattern, but without any definite nucleoli (leukoblasts of Pappenheim), were also present.

Numerous normal lymphocytes were always present. However, many of the mature lymphocytes presented atypical features, such as abundant cytoplasm, staining a very pale or deep bluish color, and a nucleus with rather heavily condensed chromatin masses (plasma cells). Occasionally nucleated red cells were present.

Study of the Imprint Preparations of the First Biopsied Lymph Node

With imprint preparations tissue cells are studied under the same conditions and with the same technique as that used for blood smears. Blood cells are usually studied in smears where they are spread out in a thin film, while tissue cells are studied in sections where they preserve their original stereometric form. It is therefore

difficult to compare the cells of sections with those of the blood smears, and this might explain those numerous incongruities in the comparison of peripheral blood cells with the tissue cells. To demonstrate any transitional forms between certain types of tissue cells and cells of the peripheral blood, one will need good imprint preparations. The technique of these imprint preparations is briefly as follows. The freshly cut surface of a small piece of tissue is touched very gently to a perfectly cleaned slide, without any pressure or smearing. The slides are dried rapidly by whipping through the air and shrinkage is thus avoided. The May-Grünwald-Giemsa staining technique will give the best results in 1½ or double concentration of Giemsa's stain because of the large number of cells. Such preparations were made from all three biopsied nodes and from the autopsied material.

Microscopic examination of the imprint preparations of the first biopsied node shows a few lymphocytes with narrow cytoplasm and a large leptochromatic nucleus having definite nucleoli. Numerous, large, reticulo-endothelial cells similar to those described in the peripheral blood are also present. The immature lymphocytes in many instances contain vacuoles in the cytoplasm and some show sharp indentations of the nuclear membrane.

Study of Imprint Preparations from the Second and Third Biopsied Lymph Nodes

These preparations present many immature lymphocytes (Fig. 6) which have the same leptochromatic nuclear pattern and narrow cytoplasm as those seen in the blood smears (Fig. 5).

Description of the Microscopic Findings of the Lymph Node from the First Biopsy

The node from the inguinal region was enlarged, measuring 1.5 by 1 by 0.5 cm. It was soft and dark grayish pink in color. The cut surface was uniformly grayish pink and showed minute hemorrhagic areas.

Microscopic examination shows that the normal structure of the lymph node is entirely obliterated; the entire structure is looser and the sharp difference between cortical and medullary portions

has disappeared. In the cortical portion only one or two follicles are recognizable; other follicles have entirely disappeared. There are places, however, where only small conglomerations of lymphocytes represent the remnants of follicles. The predominating type of cells shows syncytial arrangement (Fig. 7). These cells are characterized by a long oval and slightly acidophilic cytoplasm having an oval nucleus with little chromatin (Fig. 8), and seem to be attached to a syncytial network. There are places, however, where the attachment is looser and the cells are more rounded and have a more basophilic cytoplasm. Between these cells there are numerous, free round cells with markedly basophilic cytoplasm and heavily stained nucleus with conspicuous nucleoli. These cells are probably immature lymphocytes. The sinuses in the cortical portion are widened and filled with red cells and lymphocytes.

Description of the Node from the Second Biopsy

This biopsy was performed 4 weeks after the first biopsy. A markedly enlarged node measuring 2 by 1.5 by 1 cm. was removed from the inguinal region. It was soft and grayish red in color. The grayish pink cut surface was uniformly transparent.

Microscopic examination reveals a node that is extremely rich in cellular elements, especially in the medullary portion. The normal structure is entirely obliterated. The sinuses and intersinusoidal spaces are crowded with a dense mass of cells. These cells are characterized by a relatively large basophilic cytoplasm and a large nucleus with a dense chromatin network and are no longer arranged in a syncytial network. They seem to be immature leukemic lymphocytes.

In the cortical portion there are still fairly well defined follicles with light germinal centers containing numerous, large, oval reticular cells with pale nuclei, and scattered between these are many large lymphocytes with heavy chromatin particles and a conspicuous nucleolus. The peripheral portion of these follicles is composed of small dark lymphocytes, which are sharply demarcated from the surrounding dense mass of immature leukemic cells. Figure 9 is taken from a well preserved cortical germinal center. It shows clearly that the central portion is composed mainly of large reticular cells and that the narrow marginal portion is composed of small

lymphocytes with dark nucleoli which separate the germinal center cells from the leukemic lymphocytes. Except for the narrow marginal band of small lymphocytes the follicle and its germ center is of normal structure, and there is no evidence to indicate that the immature leukemic lymphocytes located in the interfollicular and medullary portion of the node have originated from the normal lymphocytes of the follicles or from lymphoblastic germ center cells, as claimed by many authors.

Discussion

Despite the mass of literature on the subject, the origin of lymphocytes in postfetal life is still a debated question. According to Maximow,[1] Danchakoff,[6] Weidenreich,[7] and Thiel and Downey,[8] the mesenchymal syncytium gives rise during embryonic life to all the different blood cells, including the lymphocytes. There are many different views concerning the regeneration of the lymphocytes in postfetal life. Helly,[9] Nägeli,[10] and others, maintained that regeneration was homoplastic, meaning that lymphocytes give rise to other lymphocytes. Weidenreich,[7] Downey and Weidenreich,[2] Maximow,[1] and others believed in the heteroplastic form of regeneration, claiming that the fixed cell can give rise to lymphocytes throughout life. Concerning this fixed cell there are also quite different views expressed by different authors. While Downey and Weidenreich [2] spoke of reticulum, which possesses universal potencies, Marchand [11] claimed that the periadventitial cells have embryonic potencies.

The localization of lymphocytic regeneration is still a point of disagreement. Flemming [12] regarded the clear centers of the follicles as germ centers on account of the numerous mitotic figures which they contained. Maximow [1] spoke also of the resting and active phase of germ centers. Flemming's theory was opposed by Marchand,[11] who pointed out the sharp demarcation line between the light central zone and the dark marginal portion and claimed that there are, therefore, no transitional forms between the small lymphocytes and the large cells. Hellman,[13] in a series of papers, urged against the Flemming theory that there is a quantitative disharmony between the light central zone and the dark marginal portion. One can frequently observe large germ centers with numerous mitotic figures

and very small or no marginal portion. He emphasized the fact that in cases of lymphatic leukemia with enormous lymphocytic production the light areas of the follicles have disappeared, while in certain infectious conditions there is a marked increase of germ centers without simultaneous increase of lymphocytes in the peripheral blood. Heiberg [14] pointed out that the germ centers often contain numerous pyknotic nuclei and evidences of phagocytosis (tingible bodies). Most authors believe that the germ center has a double function, regeneration and defense. Under normal conditions the germ center gives rise to lymphocytes, but under the influence of excessive demands the supply of lymphocytes in the normal sites of their formation may become exhausted. This leads to heteroplastic formation of lymphocytes from the tissue which retained its embryonic potencies.

It is known that a uniform syncytial structure characterizes the embryonic lymphatic tissue, which in the early development consists only of mesenchymal cells. Maximow,[1] Downey,[2] Marchand [11] and Klemperer [3] emphasized the morphological similarity between embryonic and adult reticulum, which suggests the possibility that the reticulum may still retain the early embryonic potencies. Maximow [1] distinguished between undifferentiated mesenchymal cells and reticulo-endothelial cells, which latter he considered as more or less differentiated cells. However, this distinction was on a functional basis, because there are no sharp morphological differences. Marchand [11] believed the periadventitial cells had universal potencies, while Herzog [15] recently divided them into two groups of perivascular cells, one of which was already differentiated along the histiocytic line (Marchand's clasmatocytes), while the other one is still multipotent (Zimmermann's pericytes, Maximow's perivascular mesenchymal cells). Von Möllendorff [16] and his pupils claim to have proved that the fibrocytes in syncytial arrangement in the loose connective tissue still have universal potencies. Klemperer [3] in 1932 considered that the undifferentiated mesenchyme of the adult organism includes the fixed "cytoplasmic reticulum" of the myeloid and lymphoid tissue, and the perivascular cells of Marchand-Herzog. He also agreed with Maximow that the "cytoplasmic reticulum" is not absolutely identical, either morphologically or functionally, with the reticulo-endothelial system of Aschoff-Kiyono, which latter is already differentiated in the phagocytic direction.

The adult organism retains a multipotent tissue, which is able to give rise to any of the blood cells. This heteroplastic blood cell formation must become logically evident in leukemias where there is the most excessive demand for blood cell formation. Lymphocytic regeneration in physiological conditions is still a debated question. Similarly, there is quite a disagreement regarding the sources of the greatly increased lymphocytes in lymphatic leukemia. Schridde [17] maintained that the disappearance of the germinal centers was due to the overgrowth of germ center cells. Nägeli [10] pointed out the fact, as a proof of the dualistic nature of the blood cells, that in myelogenous leukemia the process always starts outside of the germ centers. However, in experimentally induced extramedullary myelopoiesis, Dominici,[18] Bloom,[19] and Lang [20] showed definite evidence that myeloid transformation may start right in the centrum of the germ centers, suggesting that the omnipotent tissue is quite uniformly distributed in germ centers as well as in the pulp. Thiel and Downey,[8] Mollier [21] and Ono [22] described the development of vascular and lymph sinuses within the reticulum of spleen and lymph nodes and proved that the flat sinus endothelial cells are direct descendants of the mesenchymal syncytium and that they retain their hematopoietic potencies.

Maximow [1] gave evidence regarding the close relation of the free stem cells to the fixed reticulum cells. Ewald [23] in a case of acute leukemia, in which 95 per cent of the white blood cells were more immature than the myeloblast, found a generalized hyperplasia of the reticulum cells, and the desquamation of these immature cells was also noted. Fineman [4] obtained good evidence for the derivation of the immature lymphocytes from the reticulum in a case of subacute lymphatic leukemia. Rössle [24] reported chronic lymphatic leukemia without any involvement of lymph nodes, but with a generalized leukemic infiltration of the skin, where the hyperplastic reticulum was believed to give rise to the lymphocytes. Ungar [25] also observed a case of aleukemic lymphocytic reticuloendotheliosis in which there was evidence for the origin of lymphocytes from the fixed reticulum. Recent careful studies of numerous cases of monocytic leukemia and of leukemic reticulo-endotheliosis clearly indicate the hematopoietic activities of the reticulum cells in the Schilling type, as well as in the Nägeli type. Schwarz,[26] Hittmair [27] and many others also felt that the mesenchymal tissue

of the adult organism is able to respond to certain forms of stimulation with a marked mesenchymal cell production. Klemperer [3] recently claimed that not only in leukemias, but also in other pathological conditions (cirrhosis of the liver, Gaucher's disease), can the derivation of hemocytoblast from the generalized syncytial reticulum be observed. Tice and Jaffé [5] found in their studies of the histogenesis of leukemias that the leukemic involvement, especially in stem cell leukemias, always starts in the medullary portion of the lymph nodes.

Comment

The case herein reported presented a marked hyperplasia of the reticulum in the biopsied lymph node from the earlier stage of the leukemic involvement. At the same time, in the peripheral blood there were quite a number of large reticulo-endothelial cells in addition to immature lymphocytes. In many instances these reticulo-endothelial cells showed a nucleus with a rather dense chromatin structure resembling a nucleus of a lymphocyte (Figs. 1, 2 and 3). In a later stage the second biopsy material showed that the medullary portion was packed with a dense mass of large immature lymphocytes, while the cortical region showed more or less well preserved germ centers (Fig. 9). The subsequent disappearance of the large reticulo-endothelial cells from the peripheral blood was also noted. It must be considered, therefore, that the first involvement of the leukemic process begins with a diffuse proliferation of the reticulum. Klemperer [3] stated that the cytoplasmic reticulum, which is normally neutrophilic or slightly acidophilic, becomes more basophilic during its hematopoietic activities, and that the basophilia appears first in the perinuclear zone. The chromatin structure also becomes more condensed. That was also noted in our biopsy material stained with methyl green-pyronin (Unna-Pappenheim). We found numerous transitional forms from reticulo-endothelial cells to large lymphocytes in the imprint preparations and in the peripheral blood from the earlier stages, which later disappeared. In a later stage the medullary portion was entirely replaced by a dense mass of large cells with basophilic cytoplasm. It was only in the cortical region where a few more or less well preserved follicles were retained. Simultaneously in the peripheral blood there was a marked increase of immature lymphocytes. This

finding again indicates that in the lymphoid tissue the mesenchymal syncytium is rather uniformly distributed and that lymphocytopoiesis is not restricted to the germinal centers or to preformed germ center cells (lymphoblasts of the dualists).

The evidence of extramedullary myelopoiesis in the medulla, as well as in germinal centers, the marked monocytic production in cases of leukemic reticulo-endotheliosis and finally the transformation of the mesenchymal syncytial cells into lymphocytes, indicate the embryonic hematopoietic potency of the syncytial reticulum cells.

Summary

With three biopsies, taken at different times, the histogenetic development of a case of subacute lymphatic leukemia was followed.

In the early stages the lymph node from the inguinal region showed a diffuse hyperplasia of the syncytial reticulum cells. Many of these cells showed a beginning basophilia in the cytoplasm. At the same time the peripheral blood contained a number of larger cells with a cytoplasm that is characteristic of the reticulo-endothelial cell, but with a nucleus of lymphocytic pattern, indicating the heteroplastic origin of lymphocytes from the reticulum.

The later biopsy material from an inguinal lymph node presented a dense mass of immature lymphocytes in the medullary region, while the cortical germ centers were still preserved. The immature lymphocytes, therefore, originate in the medulla rather than in the germinal center of the follicles, and the diffusely distributed syncytial reticulum is the mother tissue for these immature lymphocytes.

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DESCRIPTION OF PLATES

PLATE 13

FIGS. 1, 2 and 3. Large reticulo-endothelial cells of the peripheral blood. May-Grünwald-Giemsa's stain. Note the abundant histiocytic cytoplasm and the slightly lymphocytic nuclear pattern. × 1800.

FIG. 4. "Transitional" cell of the peripheral blood. The nucleus is distinctly lymphocytic, while the cytoplasm is still histiocytic. × 1800.

FIG. 5. Immature lymphocytes of the peripheral blood. Note the small amount of cytoplasm and the relatively large nucleus with leptochromatic pattern. × 2400.

FIG. 6. Immature lymphocytes seen in imprint preparations from the second biopsied inguinal lymph node. Note the leptochromatic nucleus and small amount of cytoplasm. × 1400.

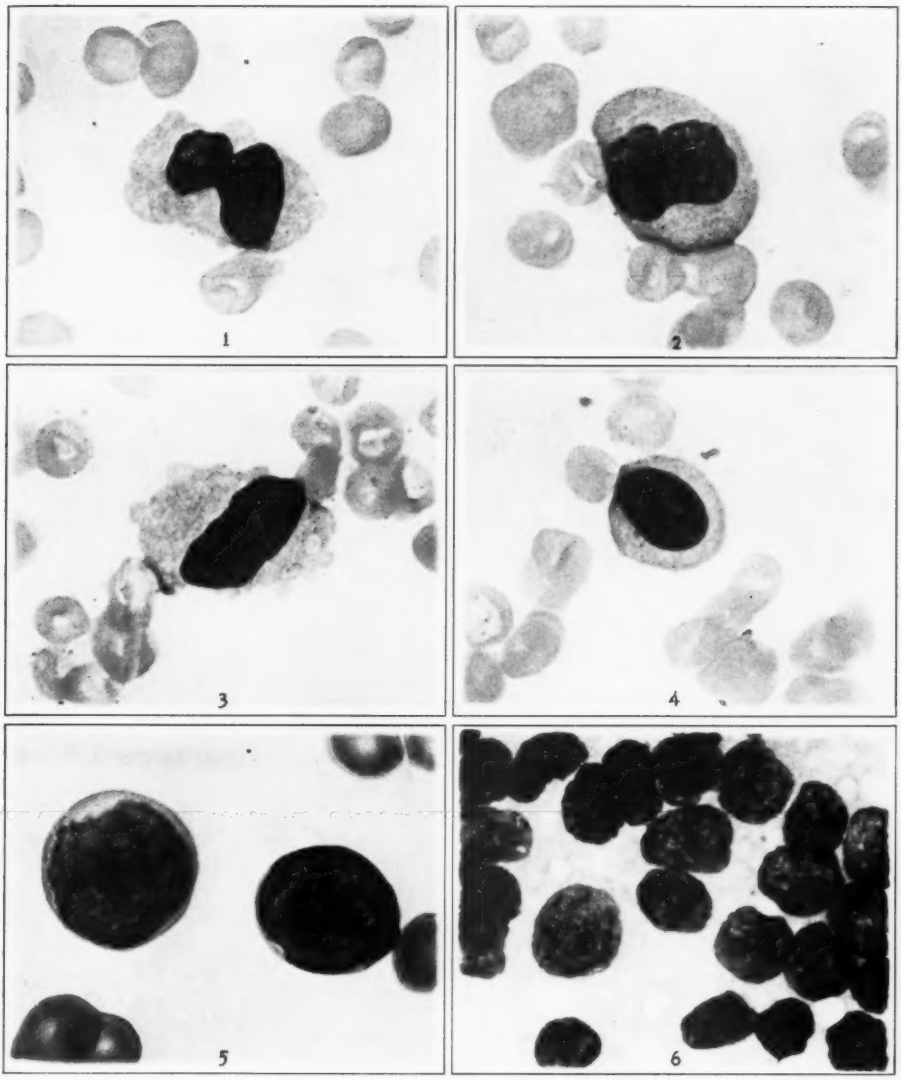
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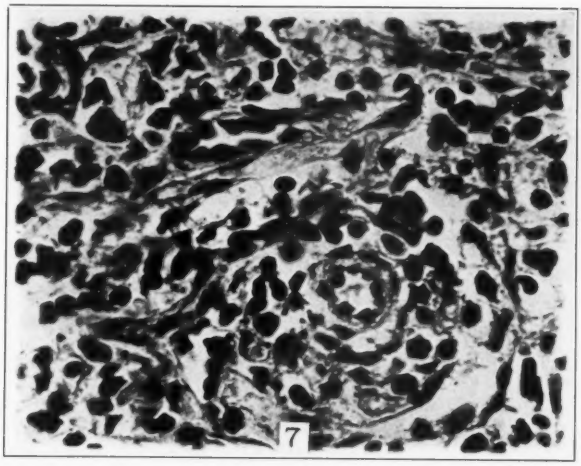
PLATE 14

FIG. 7. Lymph node from the first biopsy. The normal structure is replaced by cells in reticular arrangement. Unna-Pappenheim's stain. × 960.

FIG. 8. Lymph node from the first biopsy. The high magnification shows the oval reticular cells with pale nucleoli. Unna-Pappenheim's stain. × 1800.

FIG. 9. Lymph node from the second biopsy showing the marginal portion of a follicle. The light area indicates the germinal center, which is composed mainly of large reticular cells. A small zone of deeply staining, small lymphocytes separates the germinal center cells from the leukemic cells Dominici's stain. × 1800.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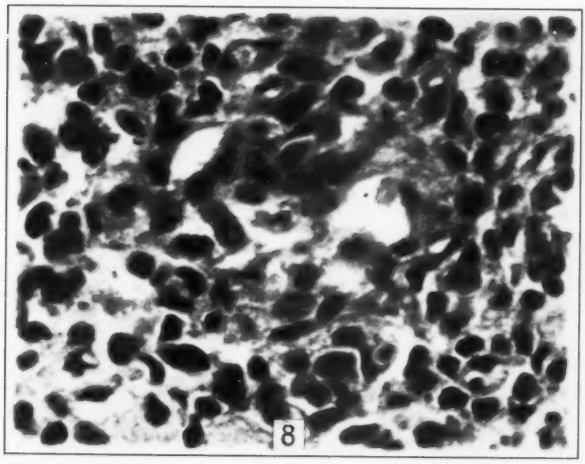
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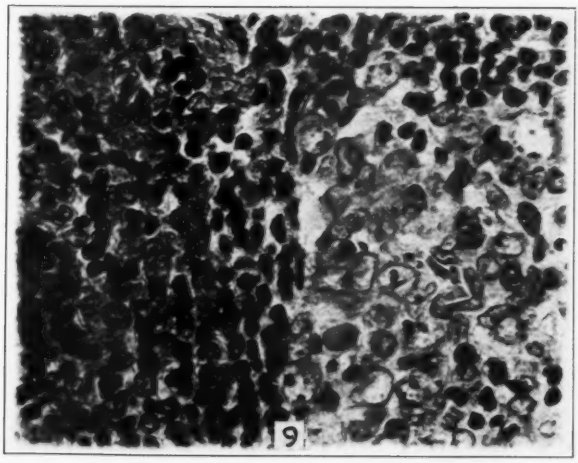
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HEPATO-ADRENAL NECROSIS WITH INTRANUCLEAR INCLUSION BODIES *

REPORT OF A CASE

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The principal purpose of this communication is to present the description of intranuclear inclusion bodies in the parenchymal cells of the liver and adrenals of a 2 weeks old premature infant in whom the chief pathological findings were a widespread necrosis of the liver and focal cortical necrosis of the adrenals. This case was brought to my attention by Prof. S. Burt Wolbach, who had never observed similar histopathology in his wide experience in the study of diseases of infancy and childhood. So far as the writer is aware no disease of similar nature has been reported in the literature.

REPORT OF CASE

Clinical History: The patient was a 7 months premature female negro infant, 40 cm. in length, weighing 3 pounds. The mother and father were in good health and there was no history of miscarriages. The patient was the mother's first baby and was 16 hours old when admitted to the hospital.

Physical examination showed a drowsy infant who, when aroused, cried lustily. There was a large, soft, non-fluctuant swelling over the right side of the skull and the anterior and posterior fontanelles were normal. There was no jaundice. Her temperature was 97° F. The clinical diagnoses were prematurity and caput succedaneum.

During the first week in the hospital the patient voluntarily ingested increasing amounts of breast milk so that by the end of the week she was taking 35 calories per pound. The swelling over the parietal region of the skull slowly disappeared and she became less active. On the eleventh day of life it was necessary to give nourishment by gavage. Her temperature gradually rose to 100° F on the twelfth day. On the thirteenth day she was transfused with 30 cc. of citrated blood obtained from her father. Four hours later her diaper was stained with blood. A small amount of blood persisted in the feces and was visible in the food which she soon began to vomit. No unusual degree of jaundice was noted. Her temperature fell to 97° F, but she died about 12 hours after the transfusion, at 14 days of age. The discharge diagnoses were prematurity and caput succedaneum.

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Autopsy Protocol

The autopsy was performed 3 hours after death.

Heart: The heart weighed 15 gm. The patent foramen ovale measured 5 mm. in diameter. A delicate row of pale red, small, granulation-like structures were found on the mitral valve.

Lungs: The right lung weighed 27 gm. and the left 22 gm. They were uniformly pink and normally crepitant except in the dependent portions where they were dark red in color and less crepitant than elsewhere. Cross-sections of the parenchyma showed numerous small red areas, which were interpreted as foci of hemorrhage rather than of pneumonic consolidation.

Spleen: The spleen weighed 10 gm., was dark red and firm.

Alimentary Tract: The stomach was small and contracted. There were a few small mucosal hemorrhages. The ileum and colon were normal.

Pancreas: Normal.

Liver: The liver weighed 75 gm. (birth weight of the liver of a normal full term infant 78 gm.). The enlargement seemed to be confined principally to the left lobe. The consistence was diminished and the surface mottled, there being numerous, irregular, grayish yellow to pale brown areas varying from less than 1 to 4 mm. in diameter. These were separated by broader zones of reddish brown parenchyma. The grayish yellow areas usually were discrete but in several instances were confluent. In the centers of several of these scattered regions were minute hemorrhagic spots. The lesions were not elevated above the plane of the surface of the liver. No exudate was present on the surface of the overlying capsule. The interior of the liver, exposed by sectioning, showed a fairly uniform distribution of the gross lesions throughout the parenchyma. No abscesses were visible.

Gall-Bladder: The gall-bladder was filled with pale brown bile less viscid than normal. Bile was expressed easily through the cystic and common ducts into the duodenum.

Kidneys: The right weighed 10 gm. and the left 9 gm. The fetal lobulations were prominent. The capsules were not adherent to the cortical substance. The cortex, medulla and pelvis of each organ were normal except for one small hemorrhagic area in the cortex of the left kidney.

Adrenals: The adrenals, which together weighed 4 gm., were normal.

Pelvic Organs: Normal.

Brain and Spinal Cord: The brain weighed 180 gm. and was considered to be normal at the time of removal. After fixation in formalin a note was made which stated that the substance of the brain was soft and fatty. The spinal cord was normal.

Bone Marrow: The bone marrow in the vertebral bodies was bright red in color.

Bacteriology: A culture of blood removed from the right auricle showed *Bacillus coli* and *Staphylococcus albus*. The same organisms were obtained from the peritoneal cavity by cultural methods.

Microscopic Study

Heart: There is a slight interstitial infiltration with polymorphonuclear leukocytes which is localized to the perivascular tissues. In rare instances the adjacent muscle fibers show minimal evidence of necrosis. No blocks were taken through the peculiar structures on the mitral valve. They may have been small "blood cysts," which are not uncommon in infancy.

Lungs: There is evidence of immature development. Many groups of alveoli are not fully distended. Other groups are overdistended and interalveolar septa often are ruptured. Occasional bronchi contain an acellular, granular, eosinophilic débris in which are numerous bacteria of variable morphology. This débris probably represents aspirated foreign material. In several alveolar spaces are extravasated red blood cells, an albuminous precipitate, asphyxial membranes and entrapped air. There is no inflammatory reaction.

Spleen: The follicles are small and of immature type and the sinusoids are distended with red blood cells. Small areas of hematopoiesis are composed largely of cells of the myeloid series. Numerous mononuclear phagocytes laden with hemosiderin are present. One small colony of cocci which seems to have stimulated no regional inflammatory reaction is found. Although the nucleoli of several of the lining cells of sinusoids are prominent there are no inclusion bodies similar to those which are found in the liver and adrenals.

Pancreas: Except for the presence of pancreatic tissue beneath the mucosa of the duodenum, no unusual histological findings are seen.

Ileum: Sections of the ileum disclose no lesions, but colonies of bacteria are seen in several vessels.

Kidneys: The only histological features of interest are those of immaturity and cloudy swelling and vacuolation of the cytoplasm of the convoluted tubules.

Urinary Bladder: No abnormal findings are noted.

Thymus: Normal.

Vertebra: No important changes are seen in the bone or bone marrow.

Brain and Spinal Cord: Blocks were taken from the cerebral cortex and the cerebellum but there are no lesions. The spinal cord shows a normal structure.

Liver: Blocks of liver were fixed in Zenker's fluid and formalin. Material which had been in formalin for 6 years was mordanted in Regaud's fluid for 48 hours. The tissue was embedded in paraffin and sections of from 5 to 7 microns in thickness were cut. The following stains and staining methods were used: hematoxylin-eosin, eosin-methylene blue, Wolbach's modification of the Giemsa stain, Gram-Weigert's method for the demonstration of bacteria, Ziehl-Neelson's carbol fuchsin stain for acid-fast organisms, Levaditi's technique for spirochetes, Mallory's anilin blue-acid fuchsin-orange G collagen stain, and Mallory's phosphotungstic acid hematoxylin.

All sections show an extensive acute necrosis with a few widely isolated clusters of viable liver cells remaining as a rule around the portal areas. The pale yellow areas which were noted in the gross specimen differ histologically from the intervening reddish brown tissue in that they represent zones where there is a most severe type of degeneration. In these regions the lobular architecture is indistinguishable. There are no continuous cords of liver cells and the sinusoidal system is disrupted. Remnants of liver cell cytoplasm, pyknotic fragments of nucleoplasm and degenerated cellular elements of the blood are fused into a conglomerate mass of débris which fills and obliterates the sinusoidal spaces and central veins. The portal structures often have succumbed, but they appear to be the last part of the structural unit to have undergone necrosis. Very little fibrin is present, although occasional necrotic vessels filled with remnants of fibrinous thrombi are found. There are no abscesses or significant local accumulations of leukocytes.

The friable reddish brown tissue which lies between the yellow

areas of necrosis shows a similar type of degeneration but the necrosis in these regions has not advanced to such a complete state of colliquation. The shadowy outlines of interrupted columns of liver cells separated by indistinct, though partly intact, sinusoids are visible amid the masses of cellular débris. Numerous extravasations of blood cells are present but most of the blood seems to be confined in the irregular, distorted sinusoidal spaces. Even though the major portion of the parenchyma is necrotic, the red blood cells appear to be much more viable in the reddish areas than in the yellow zones which have been described above. An occasional central vein is detected. These veins rarely are dilated or filled with fibrin networks in which partially degenerated blood cells are enmeshed. Portal structures and periportal connective tissue usually can be recognized but often they are involved by the necrotizing process, which seems to spread from the parenchyma, invade the periportal connective tissue and destroy, first the collagen, secondly the ducts, and finally the blood vessels. The portal veins often are dilated and, occasionally, when involved by the spread of the primary process, they are filled with fibrinous thrombi which blend at their margins with the indistinct outlines of the swollen, homogeneous, degenerated vascular wall. The reaction to this injury is very slight. The polymorphonuclear leukocytes are slightly increased in number but there is no proliferation of bile ducts or connective tissue cells.

Study of the widely separated small islands of viable liver cells and the gradual transition through various stages of degeneration in the zones bordering on the areas of necrosis discloses the most significant histological findings. These clusters of cells comprise about one-tenth of the total volume of the liver. They usually lie adjacent to the portal areas and in no instance is there a wholly intact lobule. As a rule, the architecture is almost normal, either in the center of the groups of cells or in that part which is in apposition to the periportal connective tissue. By arbitrary reconstruction of the process it would seem that the disease in the beginning must have affected the central and midzonal regions of the primary lobule.

The description of a typical viable remnant of hepatic parenchyma (Fig. 13), as studied in the sections fixed in Zenker's solution and stained by Wolbach's modification of the Giemsa stain, may suffice to exemplify a fairly uniform picture. The portion of this irregular, poorly demarcated island of cells which is adjacent to the periportal

connective tissue shows an orderly arrangement of liver cells and sinusoids. As one progresses toward the central veins an increasing number of structural alterations becomes apparent, until finally the disintegrating columns of abnormal liver cells and distorted sinusoids blend imperceptibly into the surrounding necrotic mass of liver structure.

The appearance of the individual liver cells, and especially their nuclei, is of principal interest in this study. In the periportal zone many cells are normal in size and shape. The cytoplasm is pale bluish pink, normal in structure, and the nuclei are round or oval. Delicate chromatin networks ramify throughout the nucleoplasm. The nucleoli usually are slightly eccentric in position. Among these cells, which are apparently normal, there are a few cells in which only the nuclei show abnormalities. In the first place the nuclear membranes are slightly irregular or undulate. Secondly, the chromatin networks are indistinct in the center of the nucleus and there is a definite tendency toward an accumulation of chromatin in the zone which lies adjacent to the nuclear membrane. Thirdly, most nucleoli are situated adjacent to the nuclear membrane. In these cells the relative homogeneity of normal cytoplasm is changed to a delicately granular or reticular substance. The granules are slightly acidophilic and are more deeply stained than the background of pale cytoplasm.

As one progresses from the relatively normal periportal zone of liver cells an increasing number of cytological abnormalities becomes apparent. Adjacent to the necrotic parenchyma almost all the cells exhibit the peculiar changes which characterize this malady. The unique histopathology is restricted to the nuclei, although as a rule there are attendant cytoplasmic changes of variable nature.

The nuclei for purposes of description may be divided into two groups: first, those in which there are acidophilic intranuclear bodies and, secondly, those that are characterized by abnormal basophilic intranuclear structures. A certain number of nuclei serve to exemplify the morphological and tinctorial gradations between these two principal groups.

The nuclei which contain acidophilic bodies are more numerous than the other types. The smallest bodies are found not infrequently in cells which otherwise appear to be normal. More commonly there are detectable cytoplasmic and nuclear changes. The cytoplasm

often is swollen, granular and delicately vacuolated. In the early stages the nuclei are appreciably enlarged, the chromatin networks are altered and the nucleoli are either eccentric in position or are in apposition to the nuclear membrane. In such cells minute pink granules of irregular contour appear between the partially disrupted strands of deeply basophilic chromatin which seems to be maintained distinctly apart from the acidophilic bodies (Fig. 1). The strands of chromatin gradually disappear in the center of the nucleus and preceded by the nucleolus the remnants of chromatin retreat toward the nuclear membrane, leaving a central area into which the acidophilic granules migrate (Fig. 2) so as to fuse eventually into a single, pale pink, amorphous, irregular mass of a slightly deeper red tint than the elementary bodies of which it is comprised (Fig. 3). Occasionally, heavy strands of chromatin retain their position and traverse the diameter of the nucleus in such a manner as to maintain barriers between the agglomerating unit bodies. In such instances two and rarely three distinct acidophilic masses become segregated in the divided zones (Fig. 4). As a rule a single amorphous mass occupies the center of the nucleus. As it condenses, it becomes more homogeneous and the nucleolus and chromatin retreat farther and farther so that eventually they become aligned along or intimately fused with the nuclear membrane (Fig. 5). During this stage the nucleus usually decreases in size and the nuclear membrane becomes at first serrate, and then undulate, thickened and crumpled. Finally, the fully formed inclusion body, which is deeply acidophilic, homogeneous, and well circumscribed with a sharply defined margin, lies in the center of the nucleus surrounded by a clear halo that separates almost its entire circumference from the thickened, undulate, nuclear membrane (Fig. 6).

The second variety of changes in the nuclei is almost as common as the developmental sequence which has been described above. In a few respects the two processes are similar and it is impossible to determine whether certain intranuclear bodies are a part of the first or the second theoretical sequence of changes.

In the following description an attempt has been made to reconstruct the steps in the development of the second type of intranuclear bodies. The well preserved periportal parenchymatous cells contain a few examples of the early stages. As one progresses toward the less viable central zones a great many nuclei are affected and the more

advanced stages become the most interesting feature of the histology. The earliest stage seems to be preceded by an increase in the size of the nucleus. The strands of chromatin become interrupted, chromatin material loses its affinity for basic dyes and the chromatin as well as the nucleolus seems to disappear as if by lysis. Tiny round, and often sharply defined, regularly spaced, pale blue granules appear and in almost every instance seem to fill the entire nucleus (Fig. 7). Rarely there are persistent remnants of chromatin and nucleoli which are marginated along the nuclear membrane. These delicate granules, which can be resolved definitely into distinct unit structures, occasionally are amphophilic or lightly acidophilic, but even when acidophilic their uniform punctate appearance tends to segregate them from the small, irregular pink granules which seem to form the elementary units of the inclusion bodies of the first type. Nevertheless, there are certain nuclei in which the elementary bodies of the second type are surrounded by a clear zone which partially separates them from the nuclear membrane (Fig. 8). In these nuclei one can imagine a series of gradations through which a typical inclusion body of the first type might have been formed. However, this is not apparent. There is a tendency for these small round granules to maintain their basophilic or lightly acidophilic nature and to fade into a structureless homogeneous nucleoplasm which varies from pale pink to dark blue and almost invariably fills the entire nucleus (Figs. 9 and 10). As one approaches the zone of necrosis gradual dissolution of parenchymatous cells supervenes and the homogeneous nuclei become dark blue to purplish red (Fig. 11). The nuclear membrane, at first delicate and distended, in the progressive stages becomes thickened and irregular or serrate. Finally it seems to fuse with the intranuclear plasm as the liver cell shows evidence of disintegration (Fig. 12). The cytoplasm of the liver cells that exhibit this peculiar general type of intranuclear morphology is usually pale, delicately granular, slightly vacuolated and swollen in the early stages. The cytoplasm in the later stages becomes less granular, more homogeneous and more intensely basophilic or acidophilic. In the marginal areas of necrosis where deeply basophilic and acidophilic nuclei are abundant the cytoplasmic membranes are no longer detectable and groups of liver cells seem to have flowed together to form irregular cytoplasmic masses containing several closely approximated, circular or elliptical, basophilic or

lightly acidophilic bodies, which represent the remains of the nuclei and their homogeneous content (Fig. 12). Eventually, there is complete dissolution, often preceded by a loss of differential staining reactions.

The various special stains are of no significant value, but it seems worthwhile to record briefly the staining reactions of the intranuclear bodies in tissues fixed in Zenker's fluid. In general, all granules and the fully formed acidophilic inclusions are colored pale red by Mallory's anilin blue-acid fuchsin-orange G collagen stain. The homogeneous variety of the second sequence of nuclear change is pale red to dark maroon (Figs. 10 and 11). After hematoxylin and eosin the Gram-Weigert method for the demonstration of bacteria stains the typical large intranuclear inclusions dark red or maroon (Figs. 5 and 6). The punctate granules, as described in the second series of changes, are pale purple (Figs. 7, 8 and 9), while those filled with the homogeneous substance are magenta (Fig. 11). Mallory's phosphotungstic acid hematoxylin stains the abnormal intranuclear granules a pale purple. Not infrequently they exhibit a slight orange tinge. The typical intranuclear inclusions are dark purple (Figs. 5 and 6). The homogeneous nuclei vary from pale purple to almost black (Figs. 10 and 11). The inclusions do not retain the Ziehl-Neelson carbol fuchsin stain for acid-fast organisms. The sections stained with hematoxylin-eosin and eosin-methylene blue are comparable to those which are stained with Giemsa. The intensity and sharpness of detail, as obtained by Wolbach's modification of the Giemsa stain, make these sections most satisfactory for study.

An attempt was made to demonstrate bacteria. The Ziehl-Neelson carbol fuchsin stain discloses no acid-fast organisms. The tissues which were treated by Levaditi's method for impregnation of spirochetes contain no demonstrable treponema. The Giemsa and eosin-methylene blue stains disclose rare clumps of bacilli in the liver and adrenals. They are Gram-positive, and are not situated specifically in areas of necrosis. Similar organisms unaccompanied by necrosis are found in the lungs, spleen and vessels of the wall of the ileum.

Adrenals: In the peripheral subcapsular portions of the cortex of each adrenal gland there are numerous small focal areas of necrosis. The fundamental changes in these areas are similar to those in the broad fields of degeneration in the liver. The lesions are so small that many can be included in a high dry microscopic field. All ne-

croses are acute. The primary histological changes suggest an autolytic type of parenchymal degeneration followed by disruption of sinusoids and consequent extravasation of red blood cells. In the more advanced lesions an agglomeration of the necrotic parenchymal elements and blood cells into structureless masses is characteristic. No significant inflammatory reaction is present.

One's attention, here, as well as in the liver, is attracted by the peculiar morphological alterations in the parenchymal cells. The great advantage in the study of the small early lesions is that the first stages of cellular degeneration and the progressive changes in the nuclei and cytoplasm are more clearly defined than in the liver. Intranuclear bodies of varied character which are identical with those in the liver cells are always present in the lesions. The morphological variations in the nuclear chromatin seem to precede or accompany the development of the intranuclear structures. The changes in the cytoplasm of most of the cells appear to follow the changes in the nuclei, because many cells, especially at the periphery of the lesions, have prominent intranuclear bodies without detectable abnormalities of the cytoplasm. The earliest evidence of cytoplasmic change consists of swelling, diminution in affinity for acid stains, reticulation and vacuolation. The cytoplasmic membrane is distended and the cell tends to be circular in outline. This is not accompanied by any apparent local increase in vascularity or significant disturbance of the general structural relations of the various cortical elements. In the more advanced lesions the cytoplasm is disintegrated and the cytoplasmic membrane often is disrupted. The nuclei and intranuclear bodies are almost indistinguishable. The vascularity is increased. The most severe lesions are characterized in their central portions by a fusion of the necrotic parenchymal elements and extravasated blood cells into structureless acidophilic masses. Peripherally, the progressive stages of cellular degeneration are found. In all instances the almost complete absence of leukocytic infiltration in the involved areas and the scant evidence of crystallized fibrin are consistent and inexplicable findings.

Discussion

It is not within the scope of this presentation or within the range of the writer's experience to enter at great length into the spirited

polemics that have characterized the dissertations of morphologists and bacteriologists concerning the nature and significance of "inclusion bodies." We know that there are certain viruses which have many of the properties of living matter, that these agents are ultravisible in size, that they may pass through the pores of filters which withhold ordinary bacteria, that they are capable of producing disease and that the pathology of the disease is characterized by the presence, singly or in combination, of intranuclear or intracytoplasmic masses which are called "inclusion bodies." The similarity of structure and mode of formation of inclusion bodies in different filtrable virus diseases often make it difficult to distinguish the type of virus disease by a microscopic study of the inclusion bodies. Nevertheless, there frequently are certain histological differences which may enable one to classify the virus on the basis of the morphology of the inclusions which are associated with it. These differences need not be considered fully in this presentation.

The morphology of the intranuclear bodies in the present case will allow, within the limits of our knowledge, but one conclusion. Here we must be dealing with a disease which was produced by a hitherto unknown virus, filtrable in nature and of small physical dimensions, or by a known virus which has selected unusual sites for localization and which has exhibited its pathogenicity in an unique manner. There is no justification for assuming that the unit structures, which at times could be resolved as tiny granules, were actual single microorganisms. Neither is there any justification for assuming that they are not the virus bodies or clusters of those bodies, which must have been instrumental in the production of the extensive hepatic and adrenal necrosis. In this regard it may be said that certain rickettsiae, such as the *Dermacentroxenus rickettsii* of spotted fever, have been accepted as pathogenic microörganisms. These may inhabit the nuclei of cells in ticks (Wolbach [1]). They have been cultivated in tissue cultures in the nuclei of infected mammalian mesenchymal cells (Pinkerton and Hass [2]). These microörganisms are often no larger than the elementary bodies, especially those of basophilic nature, in the nuclei of the parenchymatous cells of the liver and adrenal of the present case. The same may be said in regard to the elementary bodies of many other virus diseases. In Zenker-fixed tissues there is an undeniable resemblance between the intranuclear microörganisms of spotted fever and the intranuclear structures in

Figure 7. Not only is this true but it is quite apparent that the inclusion bodies which are formed by intranuclear masses of spotted fever rickettsiae, as demonstrated in tissue cultures, are similar to certain intranuclear inclusion bodies in various filtrable virus diseases.

It has been contended by certain authors that the acidophilic nature of inclusion bodies in general militates absolutely against the belief that they are composed of microörganisms. This does not seem entirely valid because in the present instance, as well as in herpes and experimental spotted fever, the inclusions and their constituent parts may be basophilic, amphophilic or acidophilic. Neither can such a simple criterion as the staining reaction be depended upon to indicate whether or not the virus inhabits the sphere of the inclusion body. It seems that the restrictions of microscopic vision will not allow the student to transgress the barrier, which arbitrarily has been thrown up between visible viruses which are recognized as intracellular inhabitants, and the ultravisible viruses which are characterized by the presence of intracellular inclusion bodies. A few workers, notably Goodpasture,[3] have produced evidence that the ultravisible filtrable virus may be intimately associated with the inclusion body. A further important bond of similarity is that the continued cultivation of so-called filtrable viruses, as well as the rickettsiae, depends upon the presence of living cells in the medium. It is difficult to draw hard and fast lines between the two classes of pathogenic agents, one ultravisible and characterized by inclusion bodies and the other visible and characterized by intercellular masses of microörganisms similar to inclusion bodies.

Let us compare briefly the present disease with those virus diseases that give rise to intranuclear inclusion bodies in the liver of man or animal, and with those instances in which inclusion bodies have been found in the liver independent of any established cause.

Yellow fever is a disease which presumably is caused by a filtrable virus that gives rise to necrosis of the liver and intranuclear inclusion bodies in the parenchymal cells. The inclusion bodies are very infrequent in human cases but are commonly found in the livers of monkeys in which the disease has been produced experimentally (Klotz and Belt,[4] and Cowdry and Kitchen [5]). A comparison of the inclusions of the present case with those of experimental yellow fever in monkeys revealed superficial resemblances between a few

selected inclusion bodies. On the whole the morphological changes were unlike those of yellow fever.

Intranuclear and intracytoplasmic inclusion bodies have been noted from time to time in the liver, lungs, pancreas, thyroid, adrenals, kidneys and salivary glands of infants. A group of 25 cases was reported by Farber and Wolbach.[6] The inclusions in these cases apparently were identical with those which various authors, especially Goodpasture and Talbot [7] and VonGlahn and Pappenheimer,[8] have reported and collected from the literature. A comparison of the present case with the material studied by Farber and Wolbach, and with the descriptions of the collected cases, yielded no similarities which would confuse the "protozoan-like" cells and their inclusions with the inclusion bodies of the present case. Neither has any pathogenic importance been attached to the "protozoan-like" cells with intranuclear inclusions, while it seemed reasonable to believe that the injury to the liver and adrenals of the case under discussion was due to specific localization of a virus.

McCordock and Smith [9] listed a series of infants in which there were intranuclear inclusions. Case 3 of Group 1 had foci of necrosis in the liver and suprarenal glands. There was no detailed description of the histology. It is possible that their case may have much in common with the malady described in this report.

VonGlahn and Pappenheimer [8] described intranuclear inclusion bodies in the intestine, liver and lungs of an adult who had a hepatic abscess and ulcerations of the cecum. They stated that the inclusions were identical with those that have been described in the viscera of infants. Dr. William VonGlahn has permitted the writer to study a section of the liver of their case. Neither the structure of the inclusion bodies nor the large "protozoan-like" cells which contained them was similar to the findings in the present case.

Rift Valley fever is a non-fatal virus disease which is characterized by focal necrosis in the liver of certain susceptible animals, such as sheep, goats, rats, squirrels, voles and wood mice. The inclusion bodies are restricted to the nuclei of the parenchymatous cells of the liver. The intranuclear inclusions are similar to those of yellow fever (Findlay [10]). The writer is indebted to Dr. G. M. Findlay for a section of the liver of a mouse with Rift Valley fever. A comparison with the liver of the present case disclosed similarities between many inclusion bodies. However, the resemblances were not sufficient to

admit the acceptance of close relationship or identity of the two processes.

Pacheco's parrot virus gives rise to characteristic intranuclear inclusion bodies, which may be found in the liver and other organs of parrots and parrakeets (Pacheco and Bier,[11] Rivers and Schwentker[12]). The inclusion bodies are not unlike those that have been found in yellow fever and Rift Valley fever. Although hepatic necrosis occurs in the susceptible avians, the pathogenicity of this virus for humans has not been demonstrated. The author is indebted to Dr. Thomas Rivers for a section of the liver of a parrakeet which died of this disease. The similarity between a few of the inclusions in the present case and those of the parrakeet disease did not distract from the great dissimilarity of the majority of the inclusions.

Findlay[13] described intranuclear bodies in a strain of Clacton mice. These bodies, which in many respects resembled hypertrophied nucleoli, appeared in the liver cells of Banbury mice that had been inoculated with a suspension of liver tissue of Clacton mice. Evidence was brought forward to suggest that the intranuclear bodies were caused by a filtrable virus of low pathogenicity.

Cowdry and Scott[14] described intranuclear inclusion bodies in the livers of dogs. Covell[15] found intranuclear inclusions in livers of monkeys. In each instance no ultramicroscopic virus was demonstrated.

The possibility of a localization of the herpes virus in the liver and adrenals of the present case must be considered seriously. The inclusion bodies in many respects were similar to those that arise in herpetic (herpes simplex) infections. The nature of the development of the inclusions, their morphology, their staining reactions, the presence of basophilic granules, the concurrence of basophilic and acidophilic material in several inclusions, the margination of chromatin and nucleoli, the "halo" around many of the typical well developed bodies, and other features which have been given in detail in the microscopic description, revealed an undeniable resemblance to and frequent identity with the morphology of the inclusion bodies of herpes. By no means, because of the similarity of intranuclear inclusion bodies in many diverse virus diseases, could one state that the present case illustrated an instance of herpetic infection of the liver and adrenals. However, if one were forced to select the etiological agent from the group of well established filtrable viruses, the

herpetic virus would be favored as the most probable causative factor in this singular disease. Goodpasture and Teague [16] were able to demonstrate intranuclear inclusion bodies in the parenchymatous cells of the liver and adrenals of rabbits in those areas where they had injected the herpes virus. Cowdry and Kitchen [5] obtained the same results by injection of the herpes virus into the livers of monkeys.

The portal of entry and the route of infection in the present case were not determined. It was possible that the umbilical cord may have served as the site of the primary infection, although no local lesion was demonstrated. It seemed possible that the virus may have been introduced into the infant by transfusion with the father's blood. The peculiar persistence of viruses in the tissues and fluids of humans and animals long after the disease process has subsided is well recognized. Therefore, the apparent healthy condition of the father would not militate strongly against the transmission of a virus by transfusion. There was another possibility which may be considered in the light of our knowledge of virus III infections of rabbits. This latent agent apparently lies dormant in the testes of normal rabbits. It attains virulence and produces disease only after repeated passage through the testes of rabbits. It is possible, but very unlikely, that a similar dormant species virus may have inhabited the blood of the father. As has been stated in the clinical record, the infant failed rapidly after the transfusion and died 12 hours later. This deserves repetition and emphasis only because the clue to this disease remains obscure. A careful study and analysis of similar cases may afford some inquisitive person the opportunity to transmit the disease to animals and identify the pathogenic agent. For the present the description and interpretation of the pathology of this singular malady must suffice.

Summary and Conclusions

1. A case of a 7 months premature infant, who was afflicted with a fatal disease characterized by hepato-adrenal necrosis and intranuclear inclusion bodies in the parenchymatous cells of the liver and adrenal cortex, is described.

2. It is assumed that the unique lesions must have been produced by a filtrable virus.

3. No similar case has been found in the literature.

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DESCRIPTION OF PLATES

PLATE 15

FIGS. 1–12. Photomicrographs of representative cell nuclei of the hepatic parenchyma. These contain "inclusion bodies" of various types, as described in detail in the microscopic descriptions. Similar intranuclear "inclusion bodies" were found in the focal necroses of the adrenal cortex. × 2800.

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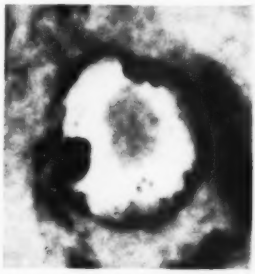

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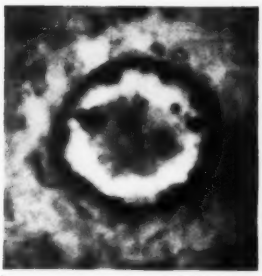

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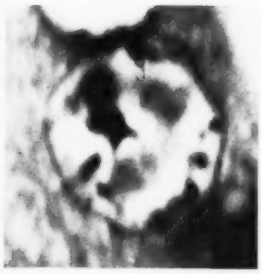

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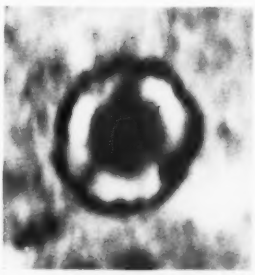

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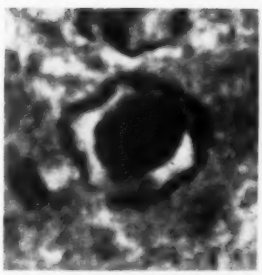

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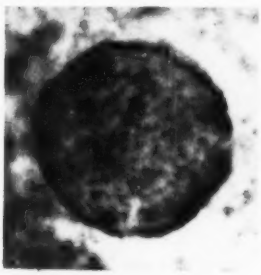

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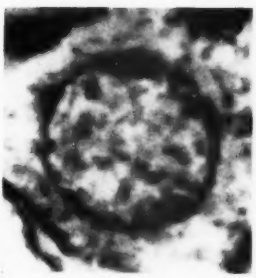

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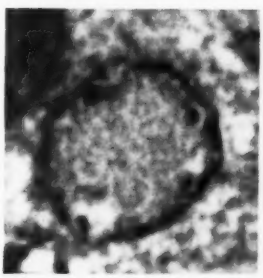

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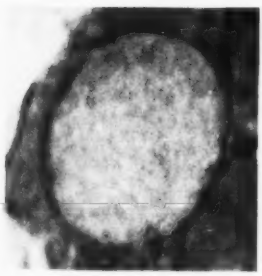

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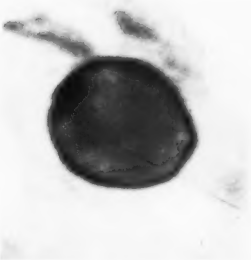

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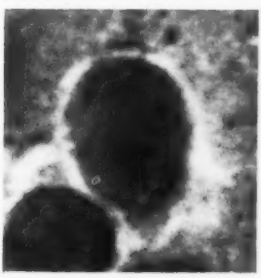

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PLATE 16

FIGS. 1–12. Camera lucida drawings of nuclei of hepatic parenchymal cells. The "inclusion bodies" which are contained in these nuclei are of the same type as those in Plate 15. Corresponding nuclei have the same numbers in the two plates (Figs. 1–12). × 3200.

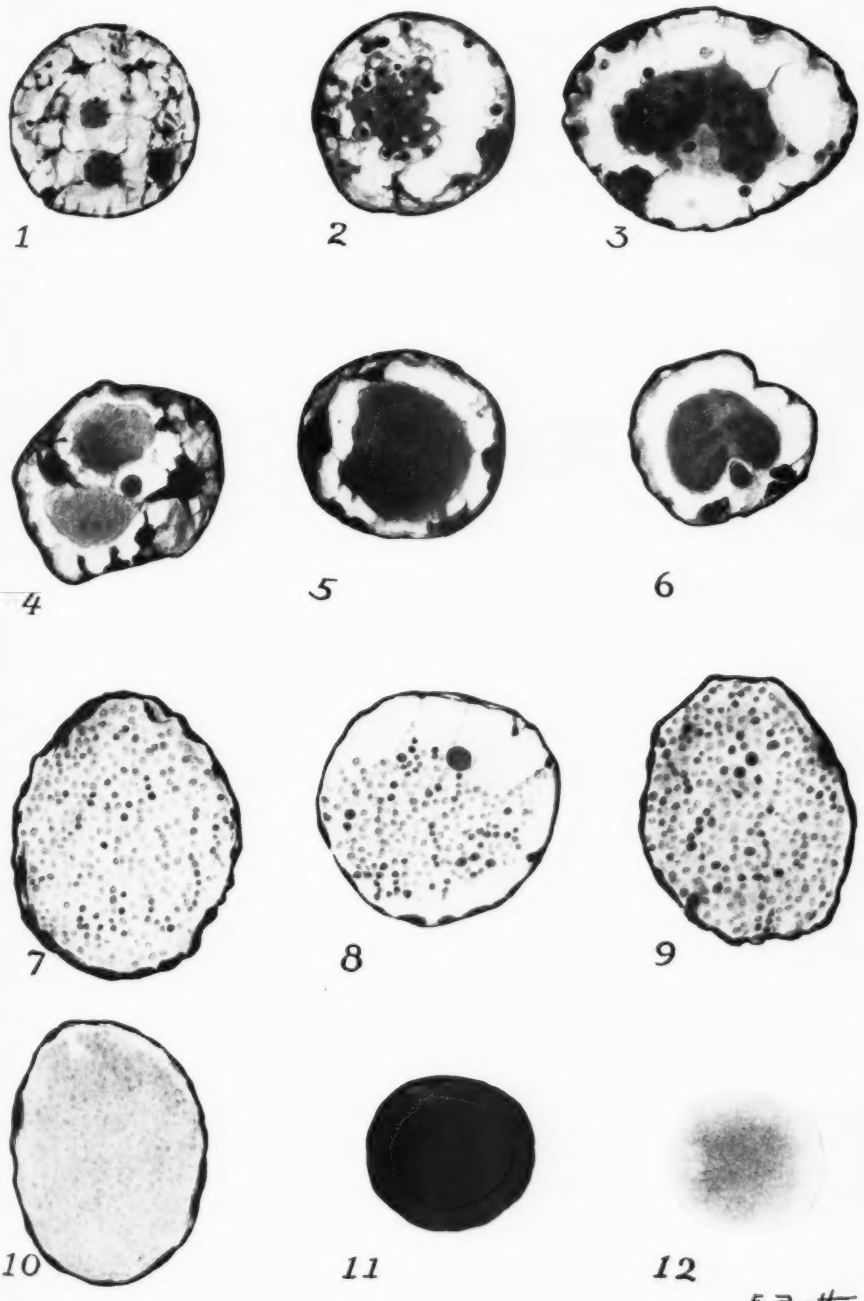
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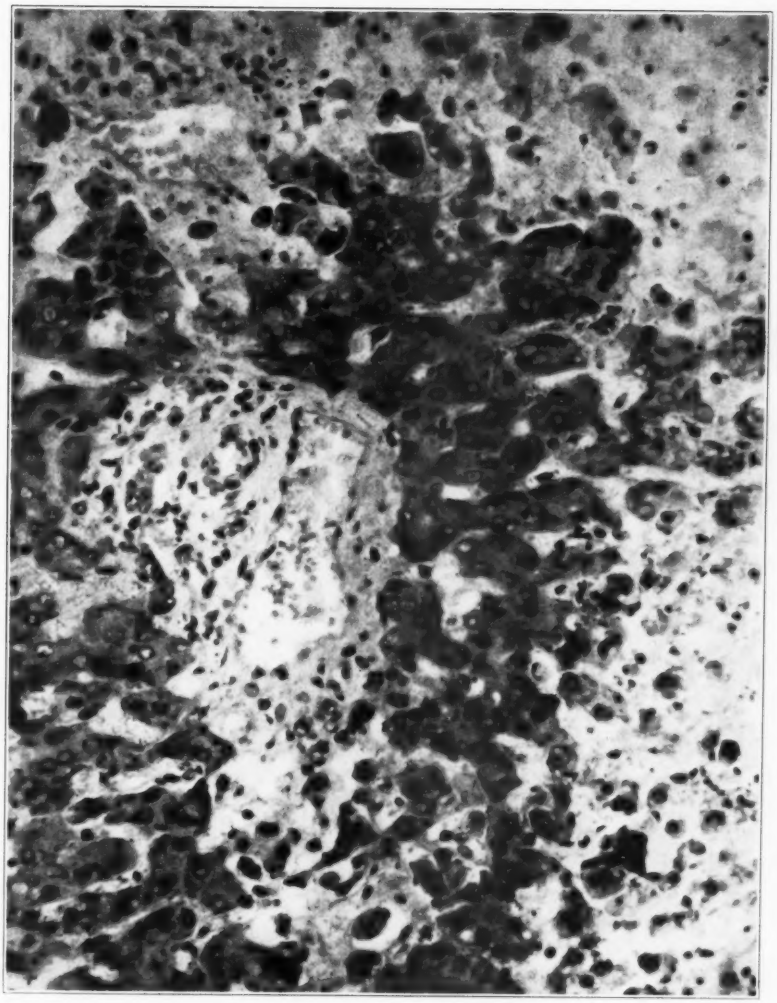
PLATE 17

FIG. 13. A photomicrograph of a representative periportal area such as was considered fully in the description of the histopathology of the liver. × 150.



13

MYOCARDIAL LESIONS IN SUBACUTE BACTERIAL ENDOCARDITIS *

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In a previous communication [1] rheumatic changes in the myocardium of children dying from subacute bacterial endocarditis were reported. Because of the fact that various other changes in the myocardium were observed during this study it seemed of interest to examine the hearts of a large group of patients, both adults and children, dying from subacute bacterial endocarditis, with special reference to myocardial changes. This seemed the more worth while in view of the discrepancy of opinions as to myocardial changes in subacute bacterial endocarditis. While Blumer [2] and others stated that the myocardium in subacute bacterial endocarditis is only rarely involved Clawson,[3,4] Libman,[5,6,7] and others emphasized the frequent occurrence of myocardial lesions.

In the following, a short abstract of the more important pertinent literature is given and the results of a study of the myocardium of thirty-five hearts of patients dying from subacute bacterial endocarditis are reported.

LITERATURE

Murray [8] in 1922 noted that early in an attack of subacute bacterial endocarditis the heart muscle shows little response to the infective processes and the patient shows no evidence of cardiac failure.

Blumer [2] in 1923 stated that the relatively slight involvement of the myocardium is a special peculiarity of subacute bacterial endocarditis. In 150 autopsies he reported, conditions of the myocardium were mentioned only thirty times. In twelve instances the recorded lesion was an evidence of toxemia, such as generalized fatty degeneration or cloudy swelling. Chronic interstitial myocarditis was noted eight times, acute myocarditis twice, small abscesses in the heart muscle three times, focal necrosis twice and infarcts twice.

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Starling [9] in 1923 observed that in subacute bacterial endocarditis emboli are frequently found, but that the myocardium is rarely involved, thereby differing from rheumatic endocarditis.

Libman [5] in 1923 reported that whenever lesions are found in the heart muscle in acute bacterial endocarditis they consist in the main of polymorphonuclear leukocytic infiltrations. In cases of subacute bacterial endocarditis, however, one finds an essentially round cell interstitial lesion, which is not present in all cases and is not specific.

Clawson [3] in 1924 analyzed 220 cases of endocarditis. The myocardium of fifty-four hearts with subacute bacterial endocarditis revealed definite indications of inflammation in thirteen instances. The character of the exudate was mononuclear in all but two in which polymorphonuclear leukocytes were found. While cardiac symptoms might not be common early in the course of the disease, at death evidences of cardiac failure are conspicuous findings. In this series evidence of cardiac failure, as manifested by edema in its various forms and passive hyperemia of the liver, was common.

Murphy and Dugan [10] in 1924 stated that the myocardium beneath the vegetations shows a rather extensive infiltration by polymorphonuclear leukocytes and round cells.

Libman [7] in 1925 reported that among twenty-seven patients with subacute bacterial endocarditis in the "bacterial-free stage" myocardial insufficiency was a determining factor in the causation of death of fourteen. Five patients revealed myocardial insufficiency alone. He also stated that "the part played by myocardial insufficiency is striking."

Bierring [11] in 1926 noted that "cardiac symptoms except for their fundamental significance are among the least prominent of all."

Thayer [12] in 1926 stated that while in acute rheumatic endocarditis the myocardial lesions are prominent, in bacterial endocarditis they are generally subsidiary. Occasionally focal areas of interstitial infiltrations with round cells or leukocytes are found in the myocardium in subacute bacterial endocarditis.

Rothschild, Sacks and Libman [13] in 1927 reported that the examination of the myocardium in subacute bacterial endocarditis discloses, in the majority of cases, focal lesions consisting of cellular infiltrations. Although these changes are seen mainly in the ventricular musculature, the infrequency of changes in the ventricular form of the electrocardiogram necessitates the assumption that they

are generally without significant effect on the intraventricular conduction.

Clawson [4] in 1928 stated that the greater frequency of abscesses in subacute bacterial endocarditis than in other forms of endocarditis evidently results from lodging of infected emboli from the valves in the myocardium. He also stated that myocarditis is even more frequent in subacute bacterial endocarditis than in acute or recurrent rheumatic endocarditis.

Hamman and Rich [14] in 1933 reported 2 cases of subacute bacterial endocarditis. In the first case the myocardium was essentially normal. The second revealed focal areas where the myocardium had been replaced by scars. There also were many minute infarcts and an occlusion of a small branch of the coronary artery by an organized thrombus. Also, fragments of infected vegetations were found in branches of the coronary arteries.

Longcope [15] in 1933 stated that some form of pathological process may be found in the heart muscle of about one-half the cases of bacterial endocarditis that come to autopsy.

Methods

Thirty-five hearts were examined. Sections from various portions of both ventricles were embedded in paraffin and stained with hematoxylin-eosin. The Gram-Weigert and the Van Gieson stains were also used. Frozen sections were often cut and stained with Sudan III to demonstrate the presence of fat. In some instances serial sections were cut from a whole block and stained with hematoxylin-eosin. The Prussian blue reaction was employed to determine the presence of iron-containing pigment.

Results

Grossly the myocardium almost invariably was softer than normal, its cut surface of a boiled appearance and the architecture obscured. Just beneath the endocardium many minute yellowish streaks were often observed, which occasionally were arranged in the form of tiger stripes. These were particularly evident in the papillary muscles of both ventricles. In some hearts the myocardium was traversed by grayish yellow and grayish red streaks, and had a peculiar speckled appearance. Occasionally, circumscribed, minute yellow nodules, or larger, soft yellow areas were encountered which were surrounded by hemorrhagic zones.

Only in 1 case could an embolus be demonstrated grossly in the coronary artery. The aortic valve in this heart was almost completely destroyed and all three cusps were practically replaced by large, soft, grayish red vegetations. Mycotic aneurysms were found in the sinus of Valsalva corresponding to the left and posterior aortic cusps. The distal portion of the circumflex branch of the coronary artery at the point of origin of the ramus marginis obtusi was occluded by an embolus which was reddish gray, soft, and similar in every respect to the vegetations on the aortic valve.

In six hearts petechial hemorrhages were encountered. More commonly the subendocardial layer was involved but occasionally the myocardium in an area at a distance from the endocardium was affected.

Histological Examination

Table I summarizes the histological findings of these thirty-five hearts.

Degenerative changes were present in all cases. The muscle fibers were swollen, their striations in some fields could not be made out at all and the sarcoplasma was distinctly granular. In many instances numerous, minute fat globules were found distributed throughout the sarcoplasma. In addition to these changes the following abnormalities were noted.

Petechial Hemorrhages: In 6 cases petechial hemorrhages in the myocardium were found microscopically. The hemorrhages were apparently very recent and the red blood corpuscles surrounded minute vessels. Neither emboli nor white cells were found in these vessels.

Acute Inflammatory Changes, Foci of Necrosis and Abscesses: Acute inflammatory changes were found in the myocardium in 15 cases. Accumulations of polymorphonuclear leukocytes were usually present in the perivascular spaces and often extended into the interstitial tissue between the heart muscle fibers. Only occasionally a few lymphocytes were seen. In 10 cases the heart muscle fibers themselves were involved. Small foci of necrosis of portions of individual muscle fibers were easily observed. The necrotic centers were often infiltrated and surrounded by polymorphonuclear leukocytes and an occasional lymphocyte and endothelial cell. In several instances clumps of bacteria were found within the necrotic

TABLE I

No. of case	Petechial hemorrhages	Acute myocarditis	Foci of necrosis and abscesses	Minute infarcts			Emboli	Perivascular, subacute, and chronic inflammation	Aschoff bodies	Perivascular fibrosis	Remarks
				Recent	Organized	Healed					
1		+	+	+	+		+				
2		+	+								
3	+				+				+	+	
4		+	+		+		+	+	+		Portion of vegetation forming embolus
5		+	+		+		+		+		
6					+	+		+	+		
7		+	+		+		+		+	+	
8					+			+	+	+	
9		+			+	+	+			+	
10				+	+	+					
11					+	+		+			
12					+	+			+	+	
13		+	+		+		+				
14	+	+	+		+		+			+	
15								+		+	
16					+	+	+				
17	+		+								
18					+						
19		+			+	+	+				
20		+	+						+	+	
21	+	+	+		+	+	+		+		Abscess in bundle of His
22					+			+			
23					+		+			+	
24		+	+				+				
25					+		+	+		+	

TABLE I (*Continued*)

No. of case	Petechial hemorrhages	Acute myocarditis	Foci of necrosis and abscesses	Minute infarcts			Emboli	Perivascular, subacute and chronic inflammation	Aschoff bodies	Perivascular fibrosis	Remarks
				Recent	Organized	Healed					
26							+	+	+	+	
27			+		+	+			+	+	
28					+	+			+	+	
29					+	+	+	+			
30					+		+	+		+	
31		+	+						+		
32					+	+	+		+		
33					+			+			
34	+	+	+		+		+			+	
35	+	+	+		+	+					

center. In 5 cases minute vessels were filled with bacteria which in turn were surrounded by polymorphonuclear leukocytes. Sometimes bacteria were seen in the peripheral portions of the lumens of the large arteries. Special stains revealed that the bacteria were invariably Gram-positive cocci arranged in small groups.

The acute interstitial changes and the minute parenchymal abscesses were almost always found in the same heart. In only 2 cases were acute interstitial changes alone noted. The common location of the abscesses were areas just beneath the pericardium and the endocardium of the left ventricle. Only occasionally was it necessary to examine many sections before these lesions were encountered.

Minute Infarcts: They were most frequently encountered. In general, three stages could be differentiated. The first, earliest stage, was only seen twice. It was characterized by areas of necrosis revealing no details of heart muscle fibers. These areas were more or less homogeneous, eosinophilic and were surrounded by clumps of cocci, polymorphonuclear leukocytes and a few red blood corpuscles. These infarcts varied, but only occasionally did they attain a conspicuous size.

The second stage was commonly encountered (in this series, twenty-eight times). This was the stage of organizing infarcts. Many spindle-shaped cells were arranged in parallel rows replacing the heart muscle fibers. Very occasionally, lymphocytes were seen scattered among these cells. Phagocytic cells were often encountered, their cytoplasm filled with a reddish granular pigment which gave a positive iron reaction. There was also a scant new formation of connective tissue fibers and several small sized blood vessels extended through this region. In many sections which showed these infarcts, emboli were encountered in their vicinity. When emboli were not seen in the section revealing organization tissue they were, as a rule, found in an adjacent section. In one instance only, a large branch of the coronary artery contained, in addition to bacteria, some necrotic and calcareous material. This material was obviously a portion of a broken-off vegetation. Surrounding this vessel many polymorphonuclear leukocytes were seen, in addition to a number of foreign body giant cells.

The third stage was characterized by the formation of dense scar tissue. Only a few nuclei were noted in this old connective tissue. A few clumps of pigment granules and an occasional phagocytic cell filled with blood pigment led to the inference that these scars represented the healed stage of small infarcts. These scars replaced heart muscle fibers and were not confined to perivascular spaces.

Perivascular Cellular Infiltrations: (Non-specific Subacute and Chronic Inflammatory Lesions): In eleven hearts inflammatory lesions were encountered which were strictly confined to the perivascular spaces. The predominating type of cell was the lymphocyte. Only occasionally a few plasma cells or endothelial cells could be found among the lymphocytes. These cellular infiltrations did not extend into the adjacent parenchyma. They were present eleven times. In only 2 cases were these lesions encountered in the same hearts which showed acute inflammatory changes. In five hearts lymphocytes were found scattered in the perivascular spaces, in addition to a new formation of fibrous tissue which still revealed fibroblastic cells. In some instances transitions between cellular infiltrations and perivascular fibrosis could be demonstrated. Multinucleated cells, or other cells resembling those seen in the Aschoff body, were not observed in these fields. The cellular elements within the perivascular fibrous regions showed no specific arrangement.

Aschoff Bodies: In 14 cases Aschoff bodies were present in the myocardium. Ten of these cases were previously reported.[1] Again it should be emphasized that whenever there was doubt as to whether or not a lesion was an Aschoff body it was not diagnosed as such. Cellular infiltrations resembling Aschoff bodies were not included. The Aschoff bodies invariably consisted of infiltrations of large cells often showing a basophilic cytoplasm containing one, two or three nuclei, a few lymphocytes and an occasional plasma cell and polymorphonuclear leukocyte. These accumulations of cells were almost always found in the vicinity of the blood vessels. Occasionally, necrotic foci or a fibrin-like material were encountered in these areas. The large cells were seen in parallel rows, often assuming a typical palisade arrangement. The internal structure of the nuclei of some of these cells (Aschoff cells) could be compared with that of a spider web. Apparently, depending upon the pressure of the surrounding tissues, the cells were either compactly arranged, the Aschoff bodies presenting an elongated appearance, or the cells were well separated from one another, the Aschoff bodies appearing rather square or round.

Perivascular Fibrosis: A new formation of connective tissue in the perivascular spaces was frequently observed. Often no cellular elements could be found in these areas even in serial sections. In several instances a few lymphocytes or histiocytic cells were recognized. Occasionally the latter showed the characteristics of the Aschoff cell.

Discussion

The petechial hemorrhages which were found in 6 cases were very recent. In these cases petechiae were also encountered in the skin or conjunctivae. It seems evident that petechiae in the myocardium have the same etiology as those found in the other locations, namely toxemia or bacteremia.

Fifteen out of thirty-five hearts revealed abscesses or foci of necrosis. It is probable that the foci of necrosis often were the precursors of the abscesses. These abscesses undoubtedly are the result of small bacterial emboli lodging in minute vessels or capillaries causing first necrosis, and secondarily abscesses. Acute inflammatory changes without formation of abscesses were encountered twice, were confined to the interstitial tissue and justify the term

acute interstitial myocarditis. Clawson stressed the greater frequency of abscesses in subacute bacterial endocarditis than in other forms of endocarditis. In his series abscesses were found in 21.5 per cent of the cases. Birch-Hirschfeld,[16] as early as 1894, mentioned ulcerative endocarditis as one of the causes of purulent myocarditis. He also stated that foci of necrosis encountered in these cases may progress to abscess formation. Very close to the necrotic foci and often in the midst of the abscesses, capillaries filled with cocci were still recognizable. If larger vessels were involved, bacteria were recognized in the peripheral portions of the lumens. This indicates that these inflammatory processes, some with small areas of central necrosis, are not comparable to infarcts but are more likely the response to the toxic products of the bacterial emboli. Mönckeberg [17] also stated that areas of necrosis did not correspond to the regions supplied by the affected vessels and that the necrotic foci therefore cannot be regarded as anemic infarcts.

The perivascular infiltrations consisting mainly of lymphocytes are noteworthy. These lesions are entirely different from those just mentioned. They also do not resemble Aschoff bodies. They are circumscribed subacute and chronic inflammatory lesions confined to the perivascular spaces and show no characteristics that give the impression of specific lesions.

The question arises as to whether or not these lesions can be regarded as Bracht-Wächter bodies. Bracht and Wächter [18] described minute and larger areas of necrosis surrounded by lymphocytes and fibroblasts in the myocardium of a rabbit injected five times at 48 hour intervals with 2 or 3 cc. of broth cultures of *Diplostreptococcus rheumaticus*. In Rabbit 2, which was injected 4 times over a period of 14 days, the myocardium revealed irregularly distributed, more or less well defined, cellular infiltrations situated mainly in the interstitial tissue. Occasionally these foci extended into the muscle fibers themselves. A few necrotic muscle fibers were seen with calcification. Most of the cells were lymphocytes. Fibroblasts, and occasionally plasma cells, were also present. In Rabbit 3, which was injected four times over a period of 16 days, the myocardium revealed long, spindle-shaped, thread-like connective tissue nuclei and streaks of fibrosis in the midst of the muscle fibers.

From this description it is difficult to determine just what a Bracht-Wächter body is. This is particularly so because of the loca-

tion of the lesions described by these authors. The lesions in Rabbit 2 were found principally in the interstitial tissue, while the lesions in Rabbits 1 and 3 were found predominating within the parenchyma. If the lesions found in Rabbit 2 are regarded as so-called Bracht-Wächter bodies, then it must be considered that their description resembles the perivascular infiltrations seen in the myocardium in these cases of subacute bacterial endocarditis. It is interesting to note, however, that Rothschild, Sacks and Libman [13] described Bracht-Wächter bodies as follows. "Examination of the myocardium in subacute bacterial endocarditis discloses in the majority of cases focal lesions consisting of cellular infiltrations (chiefly of round cells) in areas where the muscle fibers have undergone degeneration or necrosis. These are the so-called Bracht-Wächter lesions which differ from the Aschoff bodies in certain essential particulars. They are frequently inconspicuous in size and distribution, but at times they are widely diffused throughout the myocardium, and the individual lesions may assume considerable proportions."

Libman [6] stated as follows. "In cases of subacute bacterial endocarditis there is often present a focalized lesion in the myocardium known as the Bracht and Wächter lesions. These are foci which consist mainly of lymphocytes and are found in the muscle fibers themselves — the Aschoff bodies being found outside the muscle fibers. The Bracht-Wächter bodies have been reproduced experimentally, but nobody has been able to reproduce the Aschoff bodies."

Bishop *et al.*,[19] mentioned Bracht and Wächter bodies in cases of subacute bacterial endocarditis. They describe them as scattered areas of focal cellular accumulations consisting of large mononuclears, polymorphoneutrophiles and lymphocytes. The description of these authors, especially as far as location is concerned, corresponds much more to the lesions produced by Bracht and Wächter in Rabbit 3. This point will be discussed again later.

Because of the uncertainty of just what constitutes a Bracht-Wächter body, it seems wise to discard the term "Bracht-Wächter bodies" entirely and to use a rather descriptive term for lesions which by some investigators might be called Bracht-Wächter bodies. It may be mentioned in this connection that Mönckeberg,[17] probably because of the three apparently different lesions described by Bracht and Wächter, stated that these authors were not able to pro-

duce any characteristic lesions in their experiments with streptococci.

Organizing infarcts (granulation tissue) were encountered frequently. The question arises whether the described lesions are organizing infarcts or organization tissue, the result of a primary localized inflammation. The presence of blood pigment free in the tissue and within phagocytic cells is in favor of infarcts. The sparsity of inflammatory cells and the preponderance of the spindle-shaped cells also speak against a primary inflammation. Finally, the presence of emboli in the smaller branches of the coronary arteries in the vicinity of these lesions aids in determining the origin of the granulation tissue. The emboli apparently arise from broken-up vegetations. It must be emphasized, however, that often many sections have to be cut through an infarct to locate the embolus.

It is much more difficult to determine whether or not the larger fibrotic lesions which were found replacing the muscle fibers were old infarcts. Their size, the presence of an occasional phagocytic cell loaded with pigment and a few clumps of pigment free in the tissue were taken as possible evidence of old infarcts. Also, the simultaneous findings of the organizing infarcts, old fibrous scars and organized emboli are in favor of the fibrous lesions being the healed stage of infarcts. When fibrotic changes alone were found they were not designated as healed infarcts but were merely referred to in a purely descriptive manner.

The organizing infarcts seem to be the most characteristic changes in the myocardium in subacute bacterial endocarditis. Possibly some of the lesions found by Bracht and Wächter in Rabbit 3 may be interpreted as infarcts. These authors, in addition to the changes described before, also found necrotic lesions with polymorphonuclear leukocytes, fibroblasts and lymphocytes classified as possible infarcts. It is also possible that some of the lesions in the myocardium produced experimentally by Thalhimer and Rothschild [20] can be interpreted as infarcts. They described them as follows. "Later the lesions became more proliferative. Fibroblasts soon became prominent and developed rapidly into a fibrous stage. Later fibrous tissue was found surrounded by healthy muscle fibers containing a few leukocytes. Not all the fibrous areas were circumscribed. Many were diffuse, their fibers running parallel to those of the myocardium, apparently having replaced the latter. Some of the focalized

lesions had a close relationship to the small and medium sized blood vessels. Occasionally, hyaline thrombi were found." However, these authors stated that the hyaline thrombi did not occur regularly and appeared to have had no relation to the lesions.

All the hearts in this series were taken from children or young adults. Because the collaterals of the coronary arteries are not yet developed in the young, it is easily understood why emboli in small branches of the coronary arteries caused infarcts. It is also possible that the reason for the development of infarcts in these hearts lies in the simultaneous involvement of several small branches of one coronary artery. It may be of interest to point out that emboli in the coronary artery resulting from broken-down thrombi are very rare, while emboli arising from vegetation or bacterial emboli are commonly encountered histologically in these vessels in subacute bacterial endocarditis. On the other hand, an embolus was recognized grossly only once. The destruction of the aortic valve with the resulting insufficiency of this valve may have aided in the lodging of emboli in the coronary arteries.

Aschoff bodies were encountered fourteen times. In Clawson's [4] series of 60 cases of subacute bacterial endocarditis Aschoff bodies were found twenty-seven times. The significance of the findings of Aschoff bodies in subacute bacterial endocarditis was the object of a previously reported study.[1] It may again be stressed that the finding of typical Aschoff bodies in the myocardium in subacute bacterial endocarditis may be taken as evidence against the assumption that subacute bacterial endocarditis is the immune response in a previously hypersensitive patient. It would be difficult to explain why a tissue should respond simultaneously in two ways, namely with a hypersensitive reaction, of which the Aschoff body is supposed to be an example, and with an immune reaction, *i. e.*, subacute bacterial endocarditis. The Aschoff bodies were undoubtedly recent, indicating that rheumatic infection was present at the time of development of subacute bacterial endocarditis. It may also be of interest to point out that Aschoff bodies and abscesses were occasionally encountered in a single section. It may be mentioned that Thayer [12] also found Aschoff bodies associated with abscesses in the myocardium in one heart.

Perivascular areas of fibrosis were encountered fifteen times. In 6 cases they were seen in the hearts which also contained Aschoff

bodies and in 3 other cases they were present in hearts which revealed perivascular areas of non-specific subacute and chronic inflammation, but no Aschoff bodies. Only twice a perivascular fibrosis was encountered in a heart which showed both lesions. The perivascular areas of fibrosis were present in four hearts showing neither Aschoff bodies nor perivascular areas of subacute and chronic inflammation. Possibly the perivascular areas of fibrosis may represent the healing stage of both these lesions.

Summary and Conclusions

Myocardial changes were encountered in 35 cases of subacute bacterial endocarditis. These changes may be summarized as cloudy swelling, fatty degeneration, petechial hemorrhages, acute myocarditis, foci of necrosis and abscesses, areas of perivascular acute and chronic (non-specific) inflammation, minute infarcts, emboli in branches of the coronary arteries, Aschoff bodies and perivascular fibrosis. Minute infarcts were the most commonly encountered and the most characteristic lesions. Bracht-Wächter bodies are discussed and the conclusion reached that this term signifying specific lesions should be discarded because of the uncertainty of just what constitutes a Bracht-Wächter body.

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DESCRIPTION OF PLATES

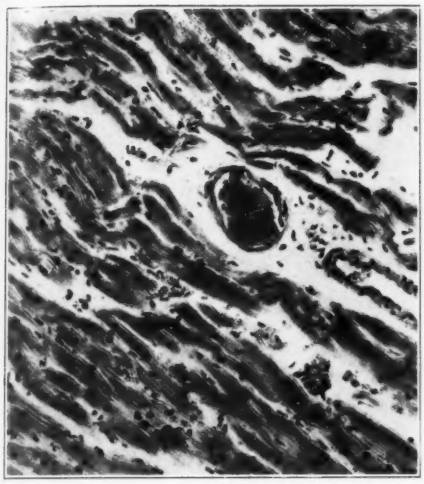
PLATE 18

FIG. 1. Recent embolus in branch of coronary artery. Hematoxylin-eosin preparation. × 150.

FIG. 2. Bacterial embolus. Note the acute inflammatory changes in the wall of the vessel. Hematoxylin-eosin preparation. × 100.

FIG. 3. Organizing embolus. Hematoxylin-eosin preparation. × 175.

FIG. 4. Focus of necrosis. Note the moderate number of polymorphonuclear leukocytes. Hematoxylin-eosin preparation. × 200.



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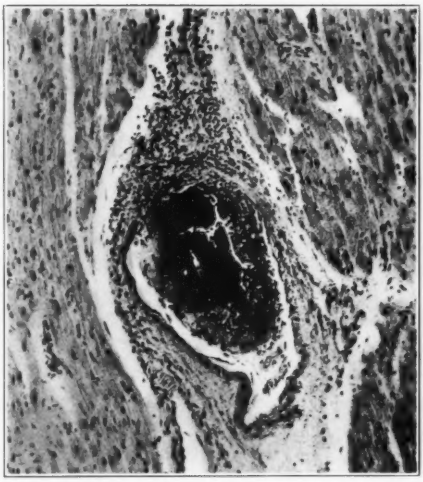

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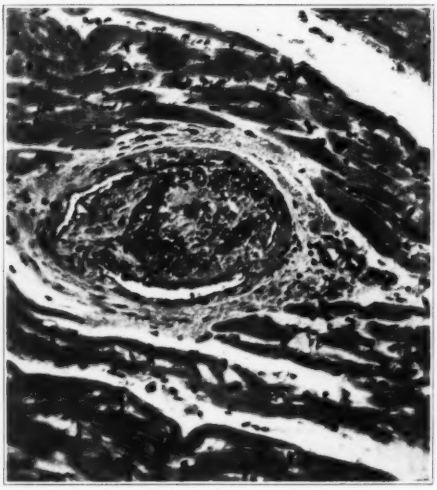

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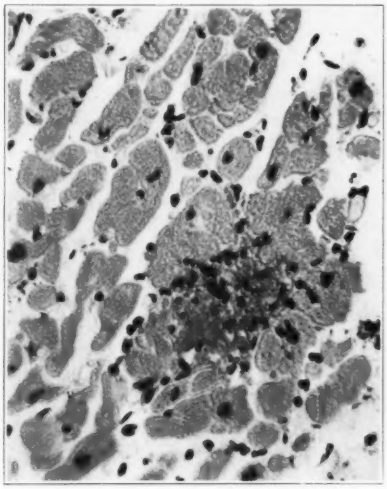

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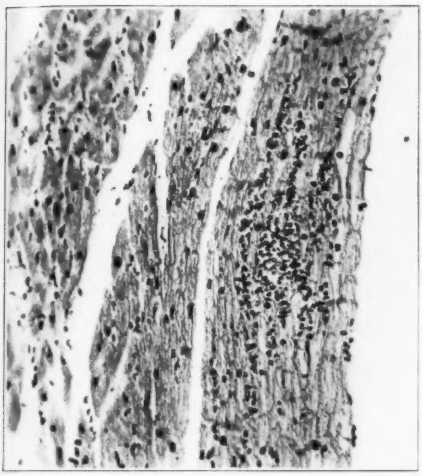
PLATE 19

FIG. 5. Abscess in the bundle of His. Hematoxylin-eosin preparation × 125.

FIG. 6. Abscess in the myocardium. Hematoxylin-eosin preparation. × 300.

FIG. 7. Area of subacute and chronic (non-specific) perivascular inflammation. Hematoxylin-eosin preparation. × 150.



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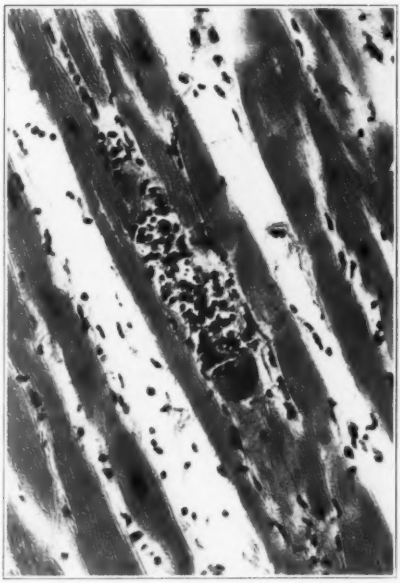

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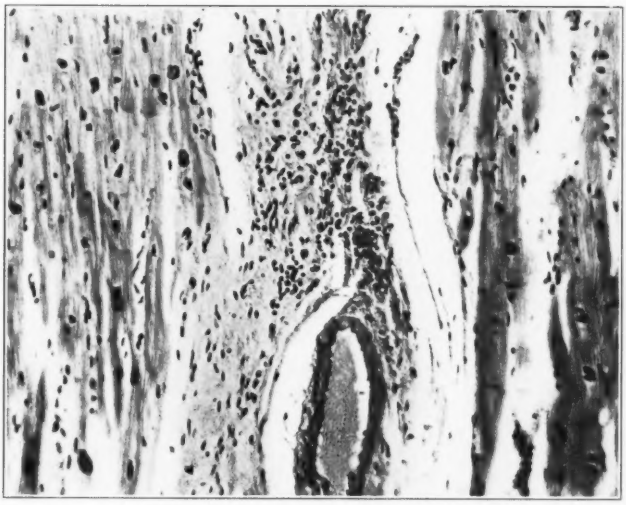

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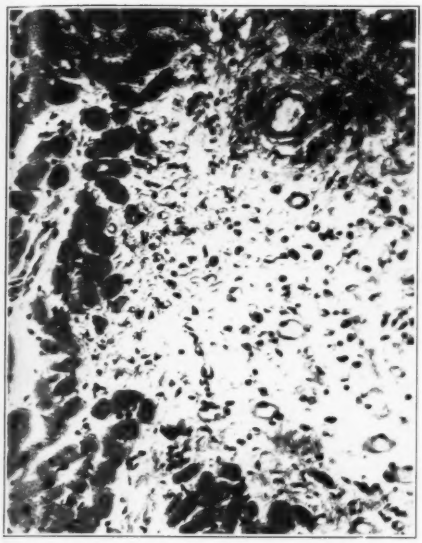
PLATE 20

FIG. 8. Organizing infarct. Note the large number of small vessels. Hematoxylin-eosin preparation. × 190.

FIG. 9. Organizing infarct, higher magnification of Fig. 8. Note the pigment-containing cells. Hematoxylin-eosin preparation. × 400.

FIG. 10. Healing infarct. Note the large number of fibroblasts and pigment-containing cells. Hematoxylin-eosin preparation. × 150.

FIG. 11. Healing infarct, higher magnification of Fig. 10. Hematoxylin-eosin preparation. × 300.



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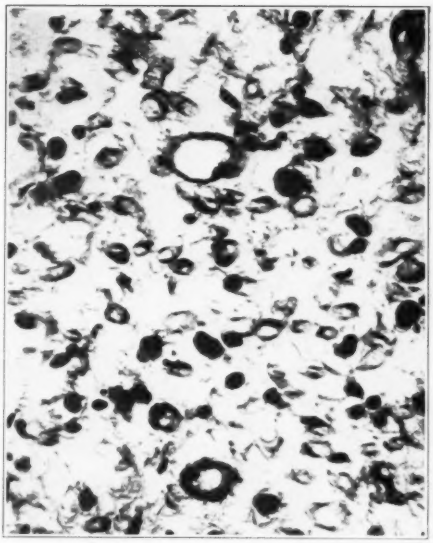

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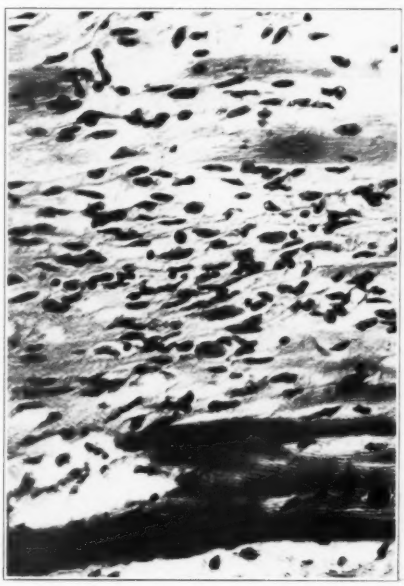

11

HEPATIC INFARCTION *

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True infarction of the liver is rare, occurring even less frequently than an uncritical review of the literature would appear to indicate. Zimmerman, in 1930, and Cioni, in 1932, attempted to collect the reported cases of hepatic infarction, but careful evaluation of the data cited in the original reports reveals the inadequacy of the criteria upon which this diagnosis was made. Among the various lesions to which this designation has been erroneously applied are such conditions as "fatty infarcts," the so-called "atrophic red infarcts" of Zahn, localized areas of hemorrhage, marked passive congestion with hepatic cell atrophy, and small intralobular areas of focal necrosis occurring in biliary stasis. The fact that these lesions differ widely in their pathogenesis and morphological characteristics has led to a misconception of several important features of the process of true hepatic infarction.

According to the generally accepted definition, an infarct is an area of necrosis due to local anemia resulting from obstruction of circulation. In the case of organs with multiple vascular supply or with abundant collateral blood vessels, the development of this lesion is necessarily conditioned by several factors which are not operative in organs with a single circulation. The approach to this problem is particularly difficult in the case of the liver, since one must critically evaluate the relative importance, in this connection, of obstruction of each of the two afferent (hepatic artery and portal vein) and the efferent (hepatic vein) vessels, all of which possess numerous collaterals and anastomotic branches.

In arriving at the diagnosis of hepatic infarction, the final decision must be based primarily upon the gross and histological characteristics of the lesion itself which, in the main, are comparable to those of similar lesions in other organs. This criterion has been adopted by

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us in reviewing the cases reported in the literature, only 20 of which have been found acceptable on this basis. Seven additional cases are described which illustrate the red, pale, and organizing phases of this lesion, and one other is presented which we believe may represent the completely healed stage of hepatic infarction.

Red Infarct

Case 1. Jeff. Hosp. H–72. M. M., a white female, aged 32 years, receiving injection treatments for varicose veins, suddenly developed vascular thrombosis and inflammatory muscular lesions of the right leg on Dec. 24, 1933. Gangrene developed and the leg was amputated under ether anesthesia 4 days later. A systolic murmur, changing later to a double murmur, was heard over the apex of the heart, which was definitely enlarged. *Streptococcus hemolyticus* was cultured from the blood stream and from the amputation stump. The patient developed marked jaundice, widely scattered petechial hemorrhages and new areas of gangrenous involvement on the left hand and foot. Death occurred Jan. 9, 1934.

Autopsy Report

The autopsy was performed 12 hours postmortem. The anatomical diagnoses were acute vegetative endocarditis of the mitral leaflets and left auricle, embolic abscesses of the myocardium, embolic occlusion of the aorta at its bifurcation and of the intrahepatic portion of the left branch of the hepatic artery, thrombosis of the uterine vessels and of the larger branches of the pulmonary artery, and infarcts of the lungs, kidneys, spleen, brain and liver. The splenic and hepatic infarcts were contaminated by gas bacillus infection.

The liver, weighing 2170 gm., was soft, friable and greasy and presented a yellowish mottling which turned green on standing. In the lateral border of the left lobe there was a reddish brown area, 10 by 3.5 by 1.5 cm., sharply demarcated from the surrounding tissue by an uninterrupted, uniformly dark red, wavy line 2–3 mm. in width (Fig. 1). This line merged into a mottled zone of vascular congestion 1–2 cm. wide, which faded out gradually into the indistinct lobular markings of the remainder of the liver. The lesion extended about 1.5 cm. into the depth of the organ and the inner limits were sharper palpably than visibly. The cut surface was dry and dull, the lobular markings were effaced, thrombosed vessels were visible and the central portion was paler than the periphery, which was separated from Glisson's capsule by a dark red, homogeneous

zone 1–2 mm. wide. A large branch of the hepatic artery, extending directly into the area of infarction, was completely occluded by a gray thrombus originating 4.5 cm. proximal to the area of necrosis. The bile ducts and larger branches of the hepatic and portal veins were patent. The gall-bladder contained 20 cc. of thick, dark bile.

Microscopic Examination

In the microscopic sections distant from the infarct the hepatic cells are slightly pigmented, granular, vacuolated and necrotic in sporadic areas; the nuclei of other cells are frequently enlarged, hyperchromatic and multiple. In the Nile blue sulphate preparations blue and reddish granules and droplets are demonstrated in hepatic and Kupffer cells in scattered small areas. The lumens of the bile ducts contain myriads of bacteria and desquamated epithelial cells.

The infarct is regularly separated from the surface of the liver by a narrow subcapsular zone of compressed viable tissue showing evidence of hepatic cell regeneration. The branch of the hepatic artery leading to the area of infarction is completely occluded by an adherent loose network of fibrin, small masses of platelets and large numbers of leukocytes, red blood cells and masses of micrococci. The accompanying branch of the portal vein is patent. Within the area of infarction there is complete necrosis of all the cells but the arrangement and structural details are well preserved. The area is diffusely stained with hemoglobin and its derivatives which along with a small amount of lipoid material is contained within Kupffer and hepatic cells around the central and sublobular veins. The perisinusoidal tissue spaces are occasionally edematous and the sinusoids are dilated and empty as a rule, but sometimes contain the shadowy outlines of erythrocytes and hyaline thrombi which alternate with masses of granular and fibrillar débris, mycotic emboli or closely packed necrotic leukocytes. The reticular walls of the sinusoids are irregular in outline, often swollen and beaded, and sometimes split, frayed and torn. The necrotic hepatic cells are somewhat distorted and deranged, and most of their nuclei are invisible while others exist in outline form only, or as poorly defined, slightly basophilic structures embedded in dense homogeneous, deeply acidophilic cytoplasm stained diffusely with hemoglobin and containing granules

and needle-shaped crystals of pigment. The outlines of the canaliculi which persist are usually accentuated by the presence of fine granules of pigment in the bordering cytoplasm. The portal radicles are frequently reduced to smudges of acidophilic material and are distorted by the presence of large vacuoles containing cocci, large bacilli and acidophilic, granular material resembling precipitated albumin. The walls of the branches of the hepatic artery and portal and hepatic veins are all necrotic and their lumens either empty or partially filled with fibrinous or leukocytic thrombi, necrotic liver cells and unidentifiable débris.

This area of necrosis is sharply demarcated from the surrounding tissue by a wide, deeply red-staining zone in which all the sinusoids are distended with a dense, homogeneous, acidophilic material, practically devoid of erythrocytes. This abrupt change in the contents and staining reactions of the sinusoids with corresponding compression of liver cords and a marked increase in the hepatic cell pigmentation are the chief distinguishing characteristics between the two zones in which the morphology and staining properties of the hepatic cells are otherwise essentially similar. More externally, the sinusoids are usually dilated and packed with phagocytic cells and erythrocytes undergoing hemolysis.

Pale Infarcts

Case 2. Jeff. Hosp. H–167. E. T., a white female, aged 55 years, was suddenly seized on Dec. 15, 1933, with excruciating thoracic pain which radiated through to the back and down both arms, and which was associated with dyspnea, cyanosis, auricular fibrillation, low blood pressure and slight fever. One month later she developed slight pretibial edema, mild jaundice and considerable tenderness over the right upper abdominal quadrant. Death occurred Jan. 21, 1934.

Laboratory Findings: Urine: specific gravity 1.026, a trace of albumin, occasional hyaline casts. White blood count 20,900. Bromsulphalein retention 40 per cent at end of 30 minutes (2 mg. dosage). Van den Bergh reaction positive direct, serum bilirubin 1.32 mg. per 100 cc.

Autopsy Report

The autopsy was performed $1\frac{1}{4}$ hours postmortem. The anatomical diagnoses were arteriosclerotic occlusion of the descending branch of the left coronary artery, and infarction of the interventricular septum and anterior and left lateral wall of the left ventricle

with extensive endocardial thrombosis. Emboli occluded the lumen of the celiac axis by two-thirds, and the right main branch of the hepatic artery completely, a short distance from its origin. Infarcts were present in the kidneys, lungs, spleen, stomach and liver.

The liver weighed 1310 gm. and was soft and friable with accentuated lobular markings. A pale, firm, slightly elevated, sharply demarcated area 7 by 5 by 2 cm., shaped like a truncated cone with its base towards the capsule, occupied a superficial position in the posterior inferior portion of the right lobe. On section the lesion was surrounded on all sides and beneath the capsule by a bright red, irregular serrated line (Fig. 2). The liver markings were absent throughout and the central portion of the necrotic area was darker and softer than the remainder, which was quite pale. A completely thrombosed branch of the hepatic artery extended directly into the lesion. The bile ducts and larger branches of the portal and hepatic veins were patent. The gall-bladder contained 30 cc. of dark, ropy bile.

Microscopic Examination

In the hepatic tissue away from the infarct there is a moderate degree of passive congestion, numerous areas of central focal necrosis and a slight degree of fatty change in some of the hepatic cells. The medial coat of the wall of the thrombosed branch of the hepatic artery is narrow and atrophied and the intima is markedly thickened by an eccentric, fibrotic and hyalinized plaque beneath which the internal elastic membrane is frayed. The lumen contains an adherent thrombus consisting of masses of fibrin, fused platelets, well preserved erythrocytes and leukocytes.

CASE 3. Phila. Gen. Hosp. 26368. F. N., a negro, aged 48 years, a chronic alcoholic, suddenly developed chills, cough, dyspnea, low blood pressure and pulmonary edema followed by a right-sided hemiplegia with fatal termination on Oct. 29, 1933. The quantitative estimation of sugar in the blood was 52 mg. per cent and of urea 50 mg. per cent.

Autopsy Report

The autopsy was performed 20 hours postmortem. The anatomical diagnoses were acute vegetative and ulcerative aortic endocarditis, diffuse suppurative myocarditis, embolic hemorrhagic abscesses

of the brain, embolism of branches of the hepatic artery, and infarcts of the liver, kidneys and spleen.

The liver weighed 1900 gm., was degenerated and studded throughout with numerous pale, wedge-shaped areas. The lobular markings were indistinct. The largest of these areas occupied a position along the lateral margin of the left lobe and was traversed by a completely occluded branch of the hepatic artery, which contained strands of fibrin, many leukocytes, erythrocytes and colonies of micrococci. The accompanying branch of the portal vein was patent.

CASE 4. Jeff. Hosp. D–1618. T. R., a white male, aged 64 years, was admitted to the hospital on June 16, 1930 with headache, fever, low blood pressure and marked infection of the jaws following extraction of teeth. There were small, red, tender nodules about several of the joints which were swollen and painful. The white cells of the blood ranged between 800 and 3900 with an average of 35 per cent polymorphonuclear leukocytes. There were 1,500,000 red blood cells and the hemoglobin was 30 per cent. The urine contained a trace of albumin and a few casts. No microörganisms grew in the blood culture. Death occurred on July 6, 1930.

Autopsy Report

The autopsy was performed 6 hours postmortem. The anatomical diagnoses were widespread petechiae of the skin, moderate diffuse subcutaneous edema, acute degeneration of the myocardium, congestion and edema of the lungs, chronic nephritis and senile arteriosclerosis of the abdominal portion of the aorta and its larger branches, and multiple infarcts of the spleen and liver.

The liver weighed 1200 gm., and showed passive congestion and central lobular coagulation necrosis, the smaller branches of the hepatic artery being markedly thickened. Scattered, small, sharply defined, grayish yellow areas not exceeding 3 cm. in width and softer in consistence than the surrounding tissue, were observed on the cut surface, especially beneath the capsule. The blood vessels were not explored but thrombosed branches of the hepatic artery, portal vein and hepatic vein were noted in direct relation to one of the areas of necrosis obtained for microscopic study; the thrombus in the branch of the hepatic artery was partially organized. The bile ducts were patulous and the gall-bladder contained a small amount of thin, dark green bile.

CASE 5. Phila. Gen. Hosp. 27587. A. B., a negro, aged 29 years, with enlargement of the heart and an apical systolic murmur died of pyemia on May 16, 1934, following incision and drainage of a perineal abscess, under local anesthesia.

Autopsy Report

The autopsy was performed 18 hours postmortem. The anatomical diagnoses were syphilitic aortitis with aneurysm formation, acute bacterial endocarditis of the aortic leaflets, focal embolic myocarditis, abscesses of the kidney and perineum, and septic thrombosis of small branches of the hepatic artery with multiple, small, pale infarcts of the liver.

The liver weighed 1700 gm. and showed portal venous congestion and periportal lymphocytic infiltration. There were several small, gray, firm, circumscribed areas 3–5 mm. in the superficial parenchyma. The blood vessels were not explored, but in the deepest portion of one of the infarcted areas obtained for microscopic section there were several necrotic vessels, one of which appeared to be a branch of the hepatic artery. These vessels were occluded and surrounded by masses of closely packed polymorphonuclear leukocytes and colonies of micrococci. Abscesses were present in the vicinity of the infarct.

COMBINED MICROSCOPIC EXAMINATION OF THE PALE INFARCTS IN CASES 2, 3, 4 AND 5

Within the areas of infarction there is complete coagulation necrosis with preservation of the architectural pattern, which is best maintained in the immediate vicinity of the portal radicles, whereas in the inner portion of the lobules autolytic changes are usually present to a slight degree. The reticulum is split, frayed and torn, and presents a thickened, lumpy, granular appearance, except along the outer rim of the lobules. The perivascular tissue spaces are edematous and the lumens of the sinusoids are usually empty or contain hematoidin burrs, a few heavy, rod-shaped bacteria and acidophilic granular débris with fragments of erythrocytes and leukocytes. Similar material is present in the Kupffer cells, which also share in the coagulative necrotic process. The lumens of the branches of the hepatic artery and portal and hepatic veins are either empty or filled to a variable degree with mottled thrombi or unrecognizable débris. Practically all the constituent cells of the portal

radicles are necrotic but the fibroblasts, bile duct epithelium and smooth muscle cells in the walls of the blood vessels are decidedly more resistant than the hepatic cells to the effects of ischemic changes.

The liver cords at the periphery of the infarct are directly continuous with others which usually form a sharply delimiting zone, 0.5–1 mm. thick around the area of complete necrosis (Fig. 3). This bordering zone presents as a rule a middle layer of coagulation necrosis merging on either side into layers of marked leukocytic infiltration, cellular disintegration, and sinusoidal thrombosis which is replaced by hyperemia as the normal liver tissue is approached. In the inner layer the necrotic material of the hepatic cells is cleared away by the action of macrophages and polymorphonuclear leukocytes, which penetrate the liver cords by way of the perivascular tissue spaces and sinusoids which are often outlined as basophilic smudges of necrotic phagocytes. The features of this bordering zone, which are most characteristic in Cases 2 and 3, are sometimes duplicated about some of the large sublobular veins, both within the areas of infarction and in the adjacent tissue.

Combined Red and Pale Infarct

Case 6. Phila. Gen. Hosp. 24707. T. R., a negro, aged 37 years, with low blood pressure, weakness and excessive thirst, died in coma on Oct. 14, 1932. The urine had a specific gravity of 1029 and contained albumin, sugar and acetone.

Autopsy Report

The autopsy was performed 5 hours postmortem. The anatomical diagnoses were acute myocardial degeneration, bronchopneumonia, splenic enlargement, portal cirrhosis with fatty metamorphosis and multiple pale and red infarcts of the liver.

The liver weighed 1730 gm. and presented the picture of coarse, nodular, portal cirrhosis. On section there were a few, small, fairly well circumscribed necrotic areas. The bile ducts were patent and the gall-bladder contained 10 cc. of dark green bile. The vessels were not explored.

Microscopic Examination

Microscopically the liver is composed of varying sized nodular areas of hepatic cells showing congestion and an advanced degree of fatty change. The central veins are out of their usual positions and

the nodules are irregular in size and arrangement and are surrounded by broad bands of hyperemic, vascular connective tissue containing chronic inflammatory cells and proliferated bile ducts. In this connective tissue several large vessels which cannot be designated as arteries or veins contain thrombi composed of slightly basophilic granular material largely devoid of cells and fibrin. The changes in the areas of necrosis show evolution from red to pale infarction, being essentially similar to those already described. There is a marked tendency for the connective tissue septa to limit the spread of the necrotic process. In several areas of early involvement the reactive changes in the bordering zone are not intense and although the hepatic cells are necrotic, hemolysis has not advanced to any degree. The latter change is followed by the paling process, which begins in two or three small areas near the center of the nodule and spreads out peripherally. The abundant fat vacuoles appear to be equally numerous within and without the areas of infarction.

Organizing Infarct

Case 7. Phila. Gen. Hosp. 24720. F. B., an insane female, aged 59 years, was subjected to cholecystostomy and incision and drainage of the pancreas under spinal anesthesia. Fat necrosis of the omentum and peripancreatic tissue was found, and death occurred one month later, Oct. 18, 1932. The urine contained sugar, albumin, and granular casts. The white cells in the blood were 27,200 per cmm.

Autopsy Report

The autopsy was performed 10 hours postmortem. The anatomical diagnoses were suppurative pancreatitis with fat necrosis of the omentum and peripancreatic tissue, sclerosis of the coronary arteries, acute myocardial degeneration, bronchopneumonia, generalized passive congestion and multiple infarcts of the liver.

The liver weighed 1170 gm., presented a nutmeg appearance, and contained a number of necrotic areas thought to be abscesses in the left margin of the left lobe. The blood vessels were not explored. The bile ducts were patulous and the mucosa of the gall-bladder was thickened and hemorrhagic.

Microscopic Examination

A section of one of these lesions contains an irregular area of hepatic infarction 1.3 cm. wide surrounded by connective tissue, ex-

cept beneath Glisson's capsule which is necrotic, markedly irregular, sunk below the general surface level of the liver and covered by an organizing peritoneal exudate. The changes in the necrotic area resembled those described under pale infarcts with certain additional features. The peripheral portion is powdered with chromatin particles of inflammatory cell nuclei in the sinusoids and contains hematoidin burrs and many acicular spaces, probably representing fatty acid crystals arranged in sheaves. The outer limits of this peripheral portion consist of a zone distinguished chiefly by the acidophilic staining reaction of its cytoplasmic masses, and the presence of long slender projections of newly formed connective tissue and capillaries penetrating at right angles from the capsule surrounding the lesion on all sides. This capsule of the infarct (Fig. 4) consists of actively organizing connective tissue infiltrated by lymphocytes, pigmented monocytes and proliferating tubular structures originating mainly from the portal radicles on its outer aspect. The tubules are round, oval, elongated and irregularly branched structures, usually with a lumen and lined by small, darkly stained cuboidal or flattened epithelial cells with hyperchromatic nuclei, but with no mitotic figures. The branches of the hepatic artery and portal vein in the portal radicles immediately outside the capsule are completely effaced by connective tissue in many instances. One large vessel which cannot be identified as either artery or vein contains an organized, canalized thrombus. The parenchyma lying adjacent to the capsule of the infarct shows dilated sinusoids, pigmentation and regeneration. Some of the arterial branches throughout the remainder of the liver show marked intimal thickening with consequent diminution in the diameter of the lumens.

Possible Healed Infarct

Case 8. Phila. Gen. Hosp. 26506. A. F., a white male, aged 63 years, died with a left-sided hemiplegia on Nov. 20, 1933. Examination of the blood and spinal fluid disclosed no evidence of syphilis.

Autopsy Report

The autopsy was performed 10 hours postmortem. The anatomical diagnoses were coronary sclerosis with old and recent myocardial infarction and endocardial thrombosis, generalized passive congestion, encysted thoracic empyema, a small peritoneal abscess,

marked atheroma with ulceration of the aorta, senile atrophy of the kidneys, possible areas of mesenteric thrombosis, recent splenic infarction and an area of possible healed hepatic infarction.

The liver weighed 1600 gm. and presented the picture of advanced chronic passive congestion with marked fatty change. On the anterior aspect of the inferior border of the right lobe there was a firm, white, depressed nodule, measuring approximately 1 cm. in diameter. The bile ducts were patent and the gall-bladder was distended with thin, brownish red bile.

Microscopic Examination

Histological sections of the nodule disclose a roughly rectangular area continuous with Glisson's capsule, submerged slightly below the general surface level of the liver and set off sharply from the hepatic parenchyma on the remaining three sides by a zone of proliferated tubular structures. It is composed of whorls and interlacing bands of comparatively acellular collagen fibrils laid down along the lines of the previous pattern of the liver (Fig. 5). The lumens of most of the sinusoids are obliterated by fine collagen fibrils, in contrast to the more densely arranged hyalinized connective tissue which has replaced the hepatic cords. Some of the sinusoids are partially patent, lined by endothelial cells, and contain normal red blood cells, monocytes, lymphocytes and polymorphonuclear leukocytes, rarely exceeding ten in number in any single sinusoid. Other structures are difficult to designate with any degree of certainty. The bile ducts are completely effaced, occasional sublobular veins are thrombosed, and a few arterial branches are thickened, usually to the point of complete occlusion. There are many small patent vessels in some of the portal radicles. This area is surrounded on three sides by a wide zone of proliferating tubular structures resembling small bile ducts and supported by loosely arranged, relatively avascular connective tissue infiltrated by lymphocytes and studded with remnants of several portal areas containing occluded hepatic arterial branches. A large portal area just beyond one corner of this outer zone contains a thrombosed canalized branch of the hepatic artery accompanied by a patent branch of the portal vein (Fig. 6). Similar arterial changes are noted in other portal areas in relation to the lesion. The branches of the arteries and veins elsewhere in the parenchyma show no thickening.

TABLE I

Reports of Hepatic Infarction

Author	Distribution in liver	Hepatic vascular lesions	Background
Chiari, H. (Case 21)	Necrosis of entire liver	Embolism of hepatic artery	Acute and chronic mitral endocarditis
Chiari, H. (Case 22)	Multiple small infarcts	Embolism of smaller branches of hepatic artery	Acute and chronic mitral endocarditis
Baldwin, F. A.	Multiple small pale infarcts with beginning organization	Thrombosis of smaller branches of hepatic artery	Aortic stenosis and regurgitation, thrombosis of right auricle, chronic passive congestion
Ruczyński, B. (Case 1)	Multiple small infarcts in right lobe	Embolism of branches of hepatic artery, more recent thrombosis of portal and hepatic veins	Vegetations in right ventricle, arteriosclerosis with ulceration and thrombus formation of the aorta
Beresnegowski, N.	Multiple small infarcts in right lobe	Surgical ligation of right branch of hepatic artery, more recent thrombosis of portal vein	Operation for carcinoma of gall-bladder
Narath, A.	Necrosis of entire left lobe, Spigelian lobe and part of right lobe	Surgical ligation of hepatic artery	Gastric resection for carcinoma of stomach
Wendel, W.	Almost total necrosis of liver	Surgical ligation of hepatic artery	Operation for carcinoma of stomach
Kretz, R.	Multiple large infarcts in both lobes	Embolism of smaller branches of hepatic artery	Acute endocarditis
Askanazy, M.	Multiple infarcts	Embolism of smaller branches of hepatic artery	Arteriosclerosis with ulceration and thrombus formation of the aorta, operated upon for mesenteric thrombosis
Mittasch, G.	Multiple infarcts	Obliterating endarteritis of hepatic artery and embolism of smaller branches	Mitral stenosis with thrombi in auricles, chronic passive congestion, arteriosclerosis
Orlandi, N. (Case 1)	Multiple small infarcts of right lobe	Embolism of smaller branches of hepatic artery, more recent thrombosis of portal vein branches	Chronic mitral endocarditis, mural thrombi in left ventricle
Orlandi, N. (Case 2)	Multiple small infarcts in both lobes	Embolism of smaller branches of hepatic artery, more recent thrombosis of portal vein branches	Vegetative mitral and tricuspid endocarditis
Orlandi, N. (Case 3)	Multiple small infarcts, small embolic abscesses	Embolism of smaller branches of hepatic artery, more recent thrombosis of portal vein branches	Osteomyelitis, pyemia with "foci" on aortic valve leaflets, chronic passive congestion

Orlandi, N. (Case 4)	Multiple infarcts in right lobe	"Primary" thrombosis of portal vein branches, "secondary" thrombosis of smaller branches of hepatic artery	Calculous cholecystitis with perforation of gall-bladder and peritonitis
Orlandi, N. (Case 5)	Multiple infarcts	"Primary" thrombosis of portal vein branches, "secondary" thrombosis of smaller branches of hepatic artery	Pylephlebitis with pylethrombosis, acute gastritis, "initial cirrhosis"
Cioni, C. (Case 1)	Large infarct in right lobe	Embolism of right branch of hepatic artery	Acute mitral and tricuspid endocarditis, mural thrombosis in left auricle, arteriosclerosis, "increase of periportal connective tissue," chronic passive congestion
Cioni, C. (Case 2)	Multiple large and small infarcts in left lobe	Septic thrombosis of left branch of hepatic artery, beginning thrombosis of portal vein	Gastric ulcer with resection and gastro-enterostomy, acute peritonitis
Graham, R. D., and Cannell, D.	Multiple large and small infarcts in left lobe	Surgical ligation of hepatic artery	Partial resection of stomach and gastrojejunostomy for carcinoma
Shann, H., and Fradkin, W. Z.	Single large infarct in right lobe with sequestration	Surgical ligation of hepatic artery	Cholecystectomy for calculous cholecystitis
Kerr, R. W.	Multiple infarcts in right lobe	Ligation of portal vein together with right branch of hepatic artery	Cholecystectomy
Lund, H., Stewart, H. L., and Lieber, M. M. (Case 1)	Large red infarct in left lobe	Embolism of large branch of hepatic artery	Acute vegetative endocarditis, septicemia
Lund, H., Stewart, H. L., and Lieber, M. M. (Case 2)	Large pale infarct in right lobe	Embolism of large branch of hepatic artery	Arteriosclerotic occlusion of left coronary artery with myocardial infarction and endocardial thrombosis
Lund, H., Stewart, H. L., and Lieber, M. M. (Case 3)	Multiple small pale infarcts	Embolism of smaller branches of hepatic artery	Acute vegetative and ulcerative endocarditis
Lund, H., Stewart, H. L., and Lieber, M. M. (Case 4)	Multiple small pale infarcts	Thrombosis of smaller branches of hepatic artery and portal and hepatic veins	Marked oral sepsis following extraction of teeth, aplastic anemia, aortic arteriosclerosis
Lund, H., Stewart, H. L., and Lieber, M. M. (Case 5)	Multiple small pale infarcts	Embolism of smaller branches of hepatic artery, thrombosis of branches of portal and hepatic veins	Acute bacterial endocarditis, pyemia
Lund, H., Stewart, H. L., and Lieber, M. M. (Case 6)	Multiple small pale and red infarcts	Thrombi in small vessels not identified as arteries or veins	Portal cirrhosis of liver
Lund, H., Stewart, H. L., and Lieber, M. M. (Case 7)	Multiple small organizing infarcts in left lobe	Organized, canalized thrombus in large vessel not identified as artery or vein	Suppurative pancreatitis, cholecystostomy with incision and drainage of the pancreas

Discussion

It is generally agreed that the life of the hepatic cell is dependent upon an adequate supply of arterial blood and is affected only to a relatively slight degree by diminution in the portal blood supply. Segall has demonstrated that necrosis of the liver results from more or less sudden total occlusion of the main stem of the hepatic artery in the absence of accessory arterial twigs or of unusually large collateral branches. Because of abundant collaterals between the right and left main branches, obstruction of either of these arteries leaves the liver in its normal condition. Those intrahepatic branches that have subcapsular ramifications necessarily have collaterals through the surface anastomoses with branches of the phrenic arteries. The frequency of occurrence and variability in distribution of these anomalous and collateral vessels preclude the possibility of generalizing in regard to the probable effects of interfering with the blood flow at any particular point in the hepatic arterial tree. However, the arterial branches which end within the liver substance and do not take any part in the subcapsular ramifications have only an extremely limited course of collateral circulation from the anastomosing small vessels in the portal sheath and around the portal vein, bile ducts and nerves; hence, obliteration of these vessels, properly designated as end-arteries, will be followed by infarction.

Occlusion of the hepatic artery or its branches was present in 25 of the 27 cases of this series; in the other 2 the vessels were not explored grossly and the thrombosed branches could not be identified as arteries or veins in microscopic sections. The interruption of arterial blood flow was considered primarily responsible for the infarction in 23 cases, in 9 of which there was secondary occlusion of the accompanying branches of the portal vein. In Orlandi's fourth and fifth cases portal vein occlusion was thought to have preceded thrombosis of the arteries. The importance of the relation of the blood vessels of the liver to hepatic infarction is clearly demonstrated in Kerr's case, in which the main branch of the portal vein and right branch of the hepatic artery were ligated, the areas of infarction being confined to the right lobe of the liver. The mechanism of hepatic artery occlusion was considered to be embolic in 14 cases, thrombotic in 5, and surgical ligation in 6. Emboli probably arose from thrombotic masses in the heart and aorta. The possible etio-

logical factors responsible for thrombosis of the hepatic artery were arteriosclerosis, cholecystitis, peritonitis, gastric ulcer, propagation of thrombi from the celiac axis, pancreatic necrosis and surgical procedures about the biliary and gastro-intestinal tracts.

Three cases of hepatic infarction occurred in cirrhotic livers. Cioni's case was due to embolism of the hepatic artery from the lesions of acute endocarditis. Orlandi's case was associated with an incipient cirrhosis, acute gastritis, pylethrombosis and secondary occlusion of the hepatic artery. In our own case of typical portal cirrhosis in the active stage, the background for the development of infarction is obscure and the large thrombosed vessels noted in histological sections could not be identified as either venous or arterial branches. Kaufmann and Rolleston and McNee believe that obliteration or thrombosis of the portal vein in cirrhotic livers may lead to the production of necrotic lesions comparable to infarcts. This seems improbable in view of the fact that in advanced cases of portal cirrhosis the condition of the hepatic circulation is comparable to that which exists following the production of an Eck fistula, and the task of supplying sufficient blood to the parenchyma for normal metabolism is relegated to the hepatic artery (McIndoe). Complete occlusion of the portal vein under these circumstances would hardly lead to infarction of the liver.

The retardation of autolytic processes within infarcted tissue in the liver resembles that in infarcts of the kidney and spleen. Orth stated that following a primary imbibition of extravasated plasma, the infarcted areas undergo a dehydration process and are slowly lysed in the course of weeks or months by the action of invading leukocytes. Although autolytic changes in the nuclei of the affected cells occur relatively early, the inhibition of total autolysis is due to the fact that the alkaline plasma, seeping into the necrotic tissue, furnishes a poor medium for the action of autolytic enzymes, but favors the action of heterolytic enzymes contained in the leukocytes along the margin of the lesion (Wells). The explanation of this retardation seems to lie in the relation between the proteolytic enzyme, cathepsin and its activator sulphydryl, which is a reduction product of glutathione in its disulphide form. Borger, Peters and Kurz found that the concentration of reduced glutathione became rapidly diminished in areas of infarction experimentally produced, indicating that instead of the disulphide being reduced to the sulphydryl it is

changed to irreversible oxidation products, the oxidation being accelerated by the alkaline reaction. With the disappearance of sulphydryl, a strong enzymatic action leading to liquefaction can, therefore, hardly take place.

The relation between fatty changes in necrotic and non-necrotic tissue of infarcted livers has been commented upon by Bainbridge and Leathes, and Cameron and Mayes, who noted a definite increase in the cellular content of free fat in lesions produced by ligation of the hepatic artery in animals. In our cases, fat droplets and vacuoles indicative of fat appeared to be identical in the area of infarction and surrounding tissue in the early stage of the lesion (Cases 1 and 6); later on (Case 2) there was a concentration of free fat along the margin which in the late organizing infarct (Case 7) contained many acicular spaces of fatty acid crystals. The explanation for the deposition of lipoidal substances in the macrophages (Ribbert), and elsewhere about the periphery of infarcts (Fischler), is assumed to lie in the persistence of cell lipase which synthesizes fatty acid and glycerol diffusing into the necrotic area with the plasma, unchecked by normal oxidative destruction of these substances (Wells).

Evidences of regeneration were present in the hepatic parenchyma in the vicinity of all the infarcted areas of our cases. These were characterized by hypertrophy and hyperchromasia, and by nuclear fission and budding, resulting in the formation of binuclear and multinuclear hepatic cells. No mitotic figures were observed. Although regeneration was regularly more active about the portal radicles than in the remaining portions of the lobules, this can probably be accounted for by the better blood supply in these areas and is not necessarily indicative of the origin of regenerating hepatic cells from bile duct epithelium. Tubular structures resembling bile ducts, and showing at first no connection with hepatic cells, grew out from the portal radicles in the viable parenchyma adjacent to the capsule of the organizing infarct. In the case of possible healed infarct these structures seemed to be continuous in some instances with the cords of liver cells in the surrounding parenchyma but did not give rise to hepatic cells within the lesion itself.

The sequence of events leading to the ultimate disposure of infarcted areas in the livers of human beings is poorly understood because the complicating factors in these cases usually precipitate an early fatal termination. In animals subjected to ligation of the he-

patic artery the necrotic lesions sometimes undergo abscess formation and calcification. In human beings large infarcted areas may become sequestrated (Shann and Fradkin), but do not appear to eventuate in abscess formation, despite the fact that they are produced by septic emboli in some instances, embolic abscesses being present in their immediate vicinity and elsewhere in the liver. The only example of possible healed infarct reported in the literature is that by Rattone. In our case we feel that the evidence favors healed infarction because of the relation of the canalized thrombosed branch of the hepatic artery to the lesion and the preservation of the architecture in the area of involvement in the presence of complete replacement by connective tissue. It is logical to assume that had the lesion resulted from abscess formation the structural pattern would have been destroyed, and if due to tuberculosis the lesion would have had more specific characteristics. The negative blood and spinal fluid Wassermann, negative colloidal gold curve, and absence of other evidences of syphilis, all argue against the possibility of gumma. The question of tumor formation does not seem to enter into the differential diagnosis.

Jaundice was present in 7 cases of this series of hepatic infarction. Factors other than the infarct itself were probably responsible for its production, since the secretory and excretory functions of the liver can be adequately maintained by a very small amount of normal hepatic parenchyma. Factors contributing to the production of hyperbilirubinemia in this condition appear to be myocardial insufficiency, infection, pulmonary infarction and cholecystitis in association with diffuse regressive lesions in the hepatic parenchyma. It is remarkable that Chiari made no mention of jaundice, although he reported total infarction of the liver. Following the production of necrotic hepatic lesions by experimental ligation of the hepatic artery in animals Betz, Asp, and Cameron and Oakley noted no disturbance in bile formation or excretion. In Graham and Cannell's collected series of 28 cases of accidental ligation of the hepatic artery in human beings jaundice was mentioned in five instances. No complicating factor was evident in Kehr's case but in the others there were calculous cholecystitis (Smith), terminal peritonitis (Ritter), hepatic traumatism (Behrend), and rupture, multiple abscesses and sequestration of the liver (Sprengle).

Summary

Infarcts of the liver may be single or multiple and generally occupy a superficial position beneath the capsule unless the area of involvement is coextensive with a whole lobe or the entire organ, a large part of which may undergo sequestration in exceptional instances. In the early stages the lesion is usually firm, red, elevated and sharply demarcated by an irregular wavy line of vascular congestion which fades gradually into the surrounding parenchyma. In the presence of portal cirrhosis the area of infarction seems relatively less firm and is limited by the coarser bands of connective tissue. Otherwise the extent of the necrosis depends roughly, in the absence of collaterals, on the distribution of the branch of the hepatic artery occluded by ligatures, emboli in the systemic circulation and thrombi resulting from infection or trauma sustained in operative procedures upon the biliary system or gastro-intestinal tract. On section the deeper border of the infarct is indented along the lines of exit of the branches of the hepatic veins and is sharper palpably than visually, although the markings of the liver are usually totally effaced in the area of involvement. A layer of viable tissue is regularly maintained immediately beneath the capsule of the liver in the early stages and assumes the appearance of rete pegs where the collateral vessels of the capsule anastomose with those in the superficial parenchyma. In the pale infarct the center may be softer and darker, indicating apparently that the hemoglobin has greater difficulty in escaping from this region, despite the fact that hemolysis seems to occur here first. The red color of the entire necrotic area may persist even after hemolysis is practically complete, owing to the diffuse staining by hemoglobin which escapes chiefly by plasmatic diffusion, the remainder being broken down into granular and fine needle-shaped crystalline pigment. Parenchymal necrosis is evident before hemolysis has occurred to any extent and, although the sinusoids are packed with red blood cells, there is little or no tendency for hemorrhage to occur into the tissue surrounding vascular structures.

The delimiting zone of an infarct is characterized at first by sinusoidal congestion and by an infiltration of phagocytic cells which rapidly increase in number. Ultimately this reactive border and a narrow strip of adjacent parenchyma, including the surface of the liver along the superficial aspect of the lesion, succumb to complete

necrosis and sinusoidal thrombosis. A thick capsule of organizing fibrous tissue then forms around the outer limits of the necrotic tissue, which is invaded only slowly by the proliferating capillaries and fibroblasts. Tubular structures resembling pseudobile canaliculi proliferate from the portal radicles in the parenchyma bordering the capsule of the infarct. Subsequently, as judged by the findings in 2 cases of possible healed infarction, the connective tissue invading the area of necrosis proceeds along the lines of the previous pattern of the liver and becomes decidedly denser in the areas formerly occupied by the liver cords and sinusoids, the normal architecture being closely duplicated with ultimate and complete organization of the necrotic area. The tubular structures proliferating on the parenchymal side of the capsule are continuous sometimes with the hepatic cells of the liver cords, but do not give rise to hepatic cells within the thick wall which they finally form around the central fibrous area.

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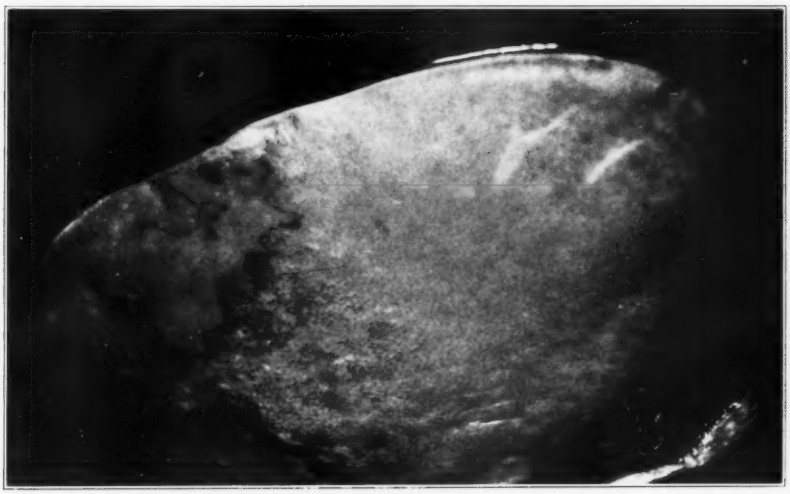
DESCRIPTION OF PLATES *

PLATE 21

FIG. 1. Case 1. Red infarct. The lesion is mottled, slightly elevated and sharply demarcated from the surrounding hepatic tissue. Photograph of gross specimen.

FIG. 2. Case 2. Pale infarct. The capsule of the liver is intact in the upper portion of the illustration, but is torn away along the right upper border. A large portal area containing a patent branch of the portal vein and two thrombosed branches of the hepatic artery lies in relation to the lower left margin of the infarcted area. Hematoxylin-eosin stain. × 2.

* An excellent reproduction of Mr. H. J. M. Nieuwenhuis' drawing of an area of anemia infarction in the right lobe of the liver following ligation of the right branch of the hepatic artery is depicted in the Atlas of Selected Cases of Pathological Anatomy by W. M. deVries, J. H. DeBussy, Ltd., Amsterdam, 1933, Plate 37.



1

2

PLATE 22

FIG. 3. Case 2. Bordering zone of infarct. The capsule of the liver with a few underlying viable hepatic cells may be seen in the upper portion of the illustration. Note the sharp line of demarcation between the zone of inflammatory cell infiltration and the area of coagulation necrosis below. × 100.

FIG. 4. Case 7. Encapsulated portion of organizing infarct showing necrotic tissue above and viable parenchyma at bottom of illustration. Note the proliferating tubular structures along the outer aspect of the capsule and the invasion of the necrotic margin by granulation tissue. × 100.

3

4

PLATE 23

FIG. 5. Case 8. Central area of possible healed infarct. The interlacing strands of connective tissue suggest liver cords and sinusoids. Portions of two large portal areas are present along the lateral margins of the illustration. Verhoeff's elastic tissue stain. × 50.

FIG. 6. The margin of the lesion shown in Fig. 5 may be seen in the left upper quadrant of the illustration. A large portal radicle containing a patent branch of the portal vein and a canalized, organized thrombosed branch of the hepatic artery leads directly into the lesion. × 50.

5

6

ANNULAR PANCREAS *

REPORT OF A CASE, WITH A SIMPLE METHOD FOR VISUALIZING THE DUCT SYSTEM

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The term "annular pancreas" or "ring pancreas" is applied to a comparatively rare developmental anomaly in which the second portion of the duodenum is encircled by a ring of pancreatic tissue. In 1933 one of us [1] reported a case of annular pancreas and summarized 39 other cases from the available literature. The embryology of the pancreas and the possible explanations for the ring portion were reviewed and illustrated, the cases were tabulated and an extensive bibliography listed. In most of the carefully described cases there was constriction of the duodenum with varying degrees of dilatation of the proximal portion of the small bowel, pylorus and stomach. Signs and symptoms of high intestinal obstruction were frequently reported, hence this anomaly must be considered in cases presenting such symptoms. The fact that Smetana [2] reported an annular pancreas in a man 74 years of age shows that it is possible to live the normal span of life with this anomaly. This patient, however, died following a gastro-enterostomy performed to relieve a progressive duodenal obstruction caused by the pancreatic ring.

We have a twofold purpose in writing this paper; first, to record another case of annular pancreas, and second, to call attention to a rapid and simple method of accurately tracing the pancreatic ducts.

In addition to the literature summarized in 1933, we have noted 3 more reports of annular pancreas.[3, 4, 5] The following case brings the total number of recorded cases to 44.

REPORT OF CASE

Clinical History: A white male, 70 years of age, noticed an enlarging painless mass in the side of his neck for 8 months. He had previously been well except for

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an illness diagnosed as coronary occlusion 3 years before, and mild diabetes recognized for 3 years.

Physical examination showed an obese, aged man with a large, tender, infiltrating tumor in the left side of the neck. The heart was enlarged, but there were no other abnormal physical findings.

Laboratory tests were normal. The urine was sugar-free, with a number of leukocytes and an occasional hyaline cast in the sediment. The blood sugar ranged from 96 to 163 mg. per cent.

The neck tumor increased rapidly in size and became very painful. Death followed progressively increasing weakness.

Autopsy Report

Autopsy, No. XXXVII–105, performed 4 hours after death, showed the body of an obese male about 70 years of age with a firm left cervical tumor 15 cm. in diameter which infiltrated the skin and muscle. Both axillae contained walnut-sized lymph nodes. Many mediastinal lymph nodes were infiltrated with white tumor and a large mass of similar tissue surrounded the upper trachea. The heart was slightly enlarged. The descending branch of the left coronary artery was occluded and there was an old scar at the apex of the left ventricle. The lungs showed extensive bronchopneumonia and pleurisy. The spleen contained small tumor nodules and there was a small accessory spleen in the mesentery. The kidneys were fused to form a typical horseshoe kidney measuring 29 by 5.5 by 3.5 cm. The right renal pelvis contained several small stones. There were a few, small, gray tumor nodules beneath the liver capsule. The stomach was normal. A flat band of pancreatic tissue 2.5 cm. broad and 0.6 to 0.8 cm. thick completely encircled the second portion of the duodenum (Fig. 1). This tongue of tissue projected to the right from the head of the pancreas posteriorly, encircled the duodenum, and again fused with the anterior portion of the head in its midportion. Anteriorly the ring was somewhat flattened over the terminal branches of the superior pancreaticoduodenal artery. The duodenum was not constricted by the ring of pancreatic tissue and there was no appreciable dilatation above it. The duodenal papilla lay in the usual position. The pancreatic duct of Wirsung measured 0.6 cm. in circumference and entered the ampulla of Vater with the bile duct. The accessory pancreatic duct of Santorini measured 0.7 cm. in circumference and opened in the left anterior wall of the duodenum 1.5 cm. above the duodenal papilla. The two ducts were united in the normal manner. A moderately large duct arose in the

left anterior tip of the ring portion, circled the duodenum to the right and posteriorly with increasing caliber, and joined the pancreatic duct 2.25 cm. from the duodenal orifice (Fig. 2, DA).

Microscopic Examination

Histological examination of the organs shows the tumor to be a lymphosarcoma. Sections of the kidney and accessory spleen are normal, except for arteriosclerotic changes. Sections from various portions of the pancreas are normal and islands of Langerhans are plentiful. One island in the tail is about five times normal size.

Anatomical Diagnoses: Lymphosarcoma involving cervical, axillary and mediastinal lymph nodes, spleen, liver and skin; bronchopneumonia; acute fibrinous pleurisy; generalized arteriosclerosis; old coronary thrombosis with infarction of the heart; thrombosis of the left ventricle and the periprostatic veins; renal calculi; biliary calculi; mild chronic cholecystitis; hypertrophy of the prostate; and the following congenital malformations: horseshoe kidney, accessory spleen and annular pancreas.

General Discussion

Embryologically, the human pancreas arises as two distinct entodermal outgrowths, the dorsal and ventral anlages, on opposite sides of the intestinal tube. As each elongates, rotation causes the ventral anlage to approach and unite with the dorsal. The dorsal anlage is large and grows across the body until it reaches the spleen. It forms the tail, the body and the ventral portion of the head of the adult gland. Its duct opens into the duodenum above the duodenal papilla but usually anastomoses with the ventral duct, which ends close beside the common bile duct in the ampulla of Vater. The ventral anlage forms a part of the head and the uncinate process of the pancreas. The ventral duct by an anastomosis with the duct of the dorsal pancreas becomes the outlet of the pancreatic duct of Wirsung. It will be noted that a large part of the dorsal pancreatic duct extending through the tail and body becomes incorporated in this main duct of Wirsung and the original outlet of the dorsal duct often atrophies but may remain functional as the accessory pancreatic duct of Santorini. It is through accurate knowledge of the arrangement of the ducts in the annular pancreas that its origin has been

traced to an anomaly of the ventral pancreatic anlage. The annular pancreas differs from the normal gland only in the ring portion, which arises from the dorsal portion of the head of the pancreas, and the ducts are comparable to those of the normal pancreas. Lecco [6] believes that the tip of the ventral anlage becomes adherent to the duodenal wall so that in the normal rotation and migration this portion of the pancreas is stretched to form the ring.

Several methods have been suggested for tracing the ducts of the pancreas, but none has proved entirely satisfactory in our hands. The ducts may be injected with a dye such as methylene blue or with mercury to facilitate sharp dissection, but either is a messy procedure and often large ducts are unexpectedly cut and true relations lost. We suggest a simple and accurate technique for demonstrating the duct system without damage to the specimen.

Injection Technique

Remove the intact pancreas and duodenum from the body. Cut across the tail of the pancreas and insert a small glass cannula into the tiny central duct, which will be easily found (Fig. 2, c). The cannula should be anchored by a ligature around the tail of the pancreas. Connect the cannula by means of rubber tubing either to a 20 cc. glass syringe, as used by Hill [7] for the injection of blood vessels, or to an injection system as described by Poth.[8] The injection material is an aqueous bismuth-acacia cream consisting of 10 per cent powdered acacia dissolved in boiling water, to which is added 20 per cent finely ground bismuth oxychloride. The mixture, when poured through a closely meshed cloth to remove the larger aggregates, is ready for use. The cream is placed in a syringe or pressure pump connected with the cannula in the duct of the tail of the pancreas and slowly injected. When the white mixture appears at the duodenal papilla, clamp and tie the tip, likewise the end of the accessory duct, if patent, and any other points of leakage. The greater the pressure of the injection, the more complete will be the filling of the smaller branches of the ducts. Remove the cannula and tighten the ligature. The radiopaque bismuth suspension clearly outlines the duct system when viewed through the fluoroscope. Place the organ in such a position that the course of the ducts is readily demonstrated and make a roentgenogram for a permanent record. Stereoscopic films are valu-

able if the duct system is complicated. The results of an injection by the Poth[8] technique are shown in Figure 2. The specimen may be fixed, sectioned and stained as usual. The bismuth will be black in the stained sections.

Discussion of the Case

Through stereoscopic roentgenographic studies of the course of the ducts in our case of annular pancreas it is evident that the ring portion had its origin in the ventral pancreatic anlage. The duct of the ring opened into the main pancreatic duct close to the ampulla of Vater and was only indirectly connected with the portion of the duct which developed in the dorsal anlage.

This patient lived to the age of 70 years with no complaints referable to his annular pancreas or other congenital anomalies. Twenty-five per cent of the reported cases of annular pancreas are associated with other congenital anomalies.

Summary and Conclusions

1. Another case of annular pancreas is recorded, bringing the total number of reported cases to 44.

2. Annular pancreas is undoubtedly a developmental anomaly of the ventral pancreatic anlage.

3. Our case was that of a man 70 years of age with several congenital anomalies but with no complaints referable to them.

4. A rapid and simple method of accurately tracing the duct system of the pancreas is described.

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DESCRIPTION OF PLATES

PLATE 24

FIG. 1. Specimen from the case reported, showing the anomalous ring of pancreatic tissue encircling the duodenum.

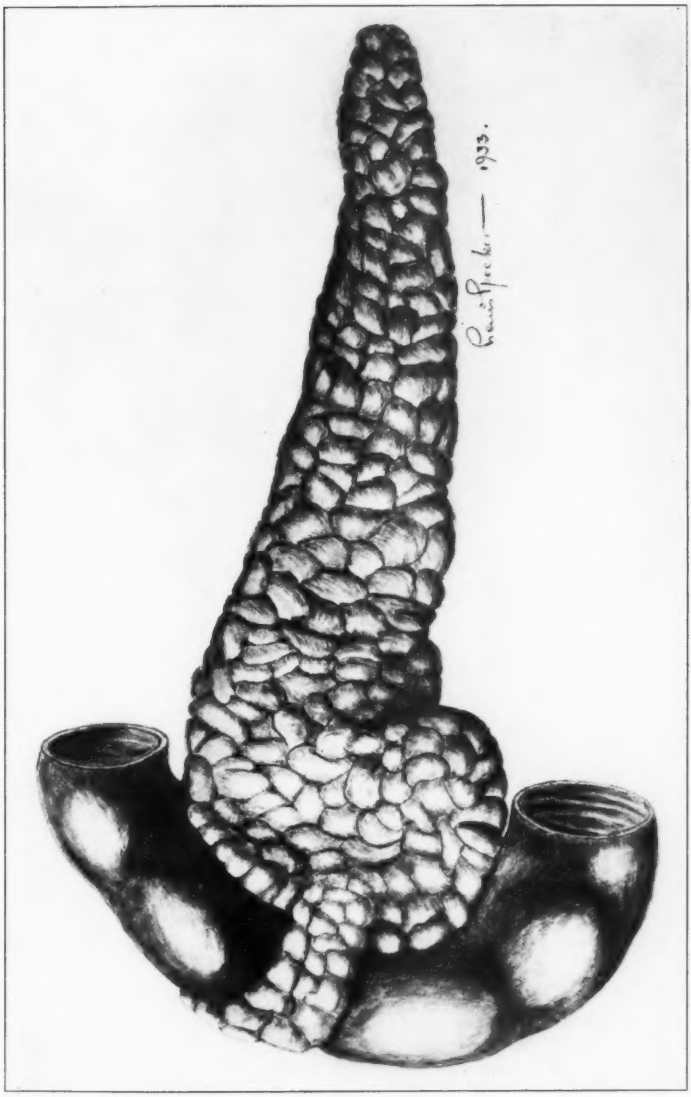

PLATE 25

FIG. 2. Roentgenogram of a case of annular pancreas after injection of bismuth cream through cannula C.

DP = duodenal papilla (ampulla of Vater)
PD = pancreatic duct of Wirsung
APD = accessory pancreatic duct of Santorini
DA = duct of the annular portion
BD = metal probe in the upper portion of the bile duct


C
BD
PD
DP
DA
APD